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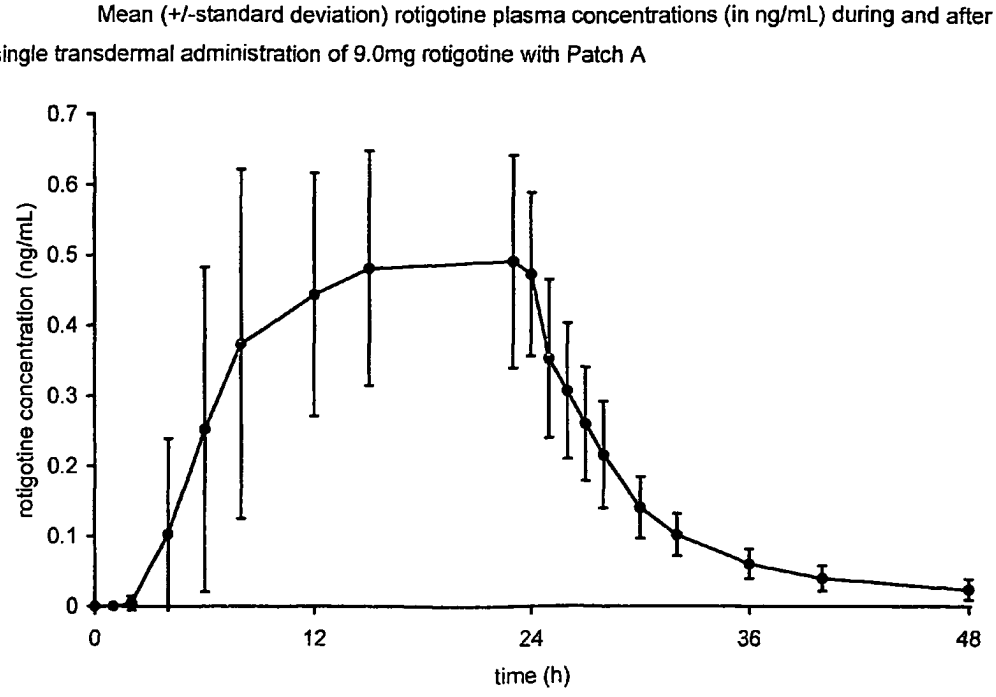

(57) Abstract: The invention provides a transdermal therapeutic system (TTS) containing rotigotine as the active ingredient. The TTS is useful in the treatment of Parkinson's Disease because it induces a pharmacokinetic profile where the rotigotine plasma level is high and stable.

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U.S. PATENT APPLICATION

for

TRANSDERMAL THERAPEUTIC SYSTEM FOR PARKINSON'S DISEASE

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TRANSDERMAL THERAPEUTIC SYSTEM FOR PARKINSON'S DISEASE

[0001] This application claims the benefit of U.S. Provisional Application Nos. 60/613,760 and 60/613,761, both filed September 29, 2004, and U.S. Serial No. 10/139,894, filed May 7, 2002, which claims the benefit of U.S. Provisional Application No. 60/363,638, filed March 12, 2002 and U.S. Serial No. 10/140,096, filed May 7, 2002 which claims the benefit of U.S. Provisional Application No. 60/363,655 filed March 12, 2002. The entire contents of these applications are herein incorporated by reference.

[0002] Various references are cited through out the application to more fully describe the subject matter of the invention. These references are hereby incorporated in their entirety.

FIELD OF THE INVENTION

[0003] The present invention relates to a skin patch (also known as a Transdermal Therapeutic System (TTS)) that delivers a sufficient amount of rotigotine, at a sufficient rate, to treat or alleviate the symptoms of Parkinson's Disease or Restless Legs Syndrome.

BACKGROUND OF THE INVENTION

[0004] The dopaminergic system uses dopamine as a neurotransmitter and plays a key role in the pathogenesis of a number of diseases including Parkinson's Disease, Alzheimer's Disease, Huntington's Disease and Schizophrenia (Seigel, G., et al, Basic Neurochemistry, 4th Ed., 1989, pp 815-822 and 864-866). The dopaminergic system has also been implicated with respect to depression (Dougherty, D., et al., J. Clin. Psychiatry, 1998; 59, Suppl 5:60-63), Restless Legs Syndrome (RLS) (Trenkwalder, C., et al. Lancet Neurol. 2005 Aug;4(8):465-75.) and Periodic Limb Movement in Sleep PLMS (O'Brien, C., CNI Review Medical Journal, Spring 1999, Volume 10, No. 1).

[0005] Parkinson's Disease is primarily a disease of middle age and beyond, and it affects both men and women. The highest rate of occurrence of Parkinson's Disease is in the age group over 70 years old, where Parkinson's Disease exists in 1.5 to 2.5% of that population. The mean age at onset is between 58 and 62 years of age, and most patients develop Parkinson's Disease between the ages of 50 and 79. There are approximately 800,000 people in the United States alone with Parkinson's Disease.

[0006] Parkinson's Disease is believed to be primarily caused by the degeneration of dopaminergic neurons in the substantia nigra. This, in effect, results in loss of tonic dopamine secretion and dopamine-related modulation of neuronal activity in the caudate nucleus, and thus in a deficiency of dopamine in certain brain regions. The resulting imbalance of neurotransmitters acetylcholine and dopamine eventually results in disease related symptoms. Although usually regarded as a motor system disorder, Parkinson's Disease is now considered to be a more complex disorder that involves both motor and nonmotor systems. This debilitating disease is characterized by major clinical features including tremor, bradykinesia, rigidity, dyskinesia, gait disturbances, and speech disorders. In some patients, dementia may accompany these symptoms. Involvement of the autonomic nervous system may produce orthostatic hypotension, paroxysmal flushing, problems with thermal regulation, constipation, and loss of bladder and sphincter control. Psychological disorders such as loss of motivation and depression may also accompany Parkinson's Disease.

[0007] Early motor deficits of Parkinson's Disease can be traced to incipient degeneration of nigral dopamine-releasing cells. This neuronal degeneration produces a defect in the dopamineric pathway that connects the substantia nigra to the striatum. As the disease progresses, refractory motor, autonomic, and mental abnormalities may develop, which implies that there is progressive degeneration of striatal receptor mechanisms.

[0008] The clinical diagnosis of Parkinson's Disease is based on the presence of characteristic physical signs, e.g., tremor, rigidity of skeletal muscles, bradykinesia, impairment of postural reflexes, and gait distrubances. The disease is known to be gradual in onset, slowly progressive, and variable in clinical manifestation. Evidence suggests that the striatal dopamine content declines to 20% below levels found in age-matched controls before symptoms occur.

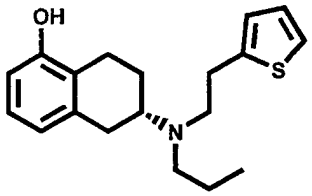
[0009] Treatment of Parkinson's Disease has been attempted with, *inter alia*, L-dopa, which still is the standard for the therapy of Parkinson's Disease. L-dopa is a compound that passes the blood-brain barrier as a precursor for dopamine and is then converted into dopamine in the brain. L-dopa improves the symptoms of Parkinson's Disease but may cause severe side effects. Moreover, the drug tends to lose its effectiveness after the first two to three years of treatment. After five to six years, only 25% to 50% of patients on L-dopa therapy maintain improvement.

[0010] Furthermore a major drawback of currently utilized therapies for Parkinson's Disease is the eventual manifestation of the "fluctuation syndrome," which results in "all-or-none" conditions characterized by alternating "on" periods of mobility with dyskinesias and "off" periods with hypokinesia or akinesia. Patients who display unpredictable or erratic "on-off" phenomena with oral anti-Parkinson therapy have a predictable beneficial response to intravenous

administration of L-dopa and other dopamine agonists, suggesting that fluctuations in plasma concentrations of drug are responsible for the "on-off" phenomena. The frequency of "on-off" fluctuations has also been improved by continuous infusions of the dopamine receptor agonists apomorphine and lisuride. However, this mode of administration is inconvenient. Therefore, other modes of administration providing a more stable plasma level would be beneficial.

[0011] As mentioned above, one treatment approach for Parkinson's Disease involves dopamine receptor agonists. Dopamine receptor agonists, sometimes also referred to as dopamine agonists, are substances which, while structurally different from dopamine, bind to dopamine receptors and trigger an effect which is comparable to that of dopamine. Due to the reduced side-effects, it is advantageous when the substances selectively bind to or interact with one or a subset of the known dopamine receptor subtypes. At present there are several classes of identified dopamine receptor subtypes, the most well characterized being the D1, D2, and D3 receptors.

[0012] One dopamine receptor agonist which has been used to treat the symptoms of Parkinson's Disease is a compound called rotigotine. Rotigotine is (6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol (CAS No. 99755-59-6) having the structure:



[0013] To date, various TTS's for the administration of rotigotine have been described. Published PCT Application No. WO 94/07468 discloses a transdermal therapeutic system containing rotigotine hydrochloride as active substance in a two-phase matrix which is essentially formed by a hydrophobic polymer material as the outer phase and a disperse hydrophilic phase contained therein and mainly containing the drug and hydrated silica. The silica enhances the maximum possible loading of the TTS with the hydrophilic salt. Moreover, the formulation disclosed in WO 94/07468 usually contains additional hydrophobic solvents, permeation-promoting substances, dispersing agents and, in particular, an emulsifier which is required to emulsify the aqueous solution of the active principle in the lipophilic polymer phase. A TTS prepared by using such a system has been tested in healthy subjects and Parkinson patients. The average drug plasma levels obtained by using this system were around 0.15 ng/mL with a 20 cm^2 patch containing 10 mg rotigotine hydrochloride. This level is considered too low to

achieve a truly efficacious treatment or alleviation of the symptoms related to Parkinson's Disease.

[0014] Various further transdermal therapeutic systems have been described in Published PCT Application No. WO 99/49852. The TTS used in this patent application comprises a backing layer, inert with respect to the constituents of the matrix, a self-adhesive matrix layer containing an effective quantity of rotigotine or rotigotine hydrochloride and a protective film which is removed before use. The matrix system is composed of a non-aqueous polymer adhesive system, based on acrylate or silicone, with a solubility of rotigotine of at least 5% w/w. The matrix system is essentially free of inorganic silicate particles. In Examples 1 and 2 and in FIG. 1 of WO 99/49852, two transdermal therapeutic systems are compared. These are based on acrylate or silicone adhesives. FIG. 1 of WO 99/49852 shows that a silicone patch releases about the same amount of active principle through the skin as an acrylate patch. This has been demonstrated by the almost identical drug flux rates in an *in vitro* model, independent of the adhesive test system employed. Therefore an identical flux rate through human skin was expected.

[0015] It should be noted that the drug content of the silicone patch used in WO 99/49852 was lower than the drug content used in the acrylate patch. This merely reflects the difference in drug release capacity , however, in the respective polymeric silicone and acrylate adhesives used in Examples 1 and 2 of the published PCT application, respectively. While the acrylate system is able to dissolve more drug than the silicone system, silicone allows for a faster release of the drug to the skin. As these two effects compensate each other, it has been thought that the acrylate and the silicone system used in WO 99/49852 are about equivalent in the obtainable drug plasma levels and, hence, in therapeutic efficacy.

[0016] The shortcomings of the silicone formulation disclosed in WO 94/07468 have led to clinical tests (safety and pharmacokinetic studies) of only the acrylate-based TTS of Example 1 of WO 99/49852. The mean steady flux rate across human skin *in vitro* of this TTS amounted to 15.3 $\mu g/cm^2/h$. Even the acrylate-based TTS, however, exhibited unsatisfactory plasma levels of rotigotine that are too low to allow for a really efficacious treatment of Parkinson's Disease. A 30 mg (20 cm^2) patch only yielded a mean maximum plasma concentration of 0.12 ng/mL, while a 5 cm^2 patch containing 7.5 mg yielded a mean maximum plasma concentration of 0.068 ng/mL. Again, such values are too low to provide a real therapeutic progress in the treatment of Parkinson's Disease. In sum, neither the 20 cm^2 silicone patch disclosed in WO 94/07468 nor the 20 cm^2 acrylate patch disclosed in WO 99/49852 provided sufficient drug plasma levels to provide a satisfactory therapeutic effectiveness in the treatment of Parkinson's Disease.

[0017] The Restless Legs Syndrome (RLS) is a neurological disease that expresses itself as a false sensation in the legs accompanied by a strong kinetic urge. Symptoms of RLS include tingling, pulling, aching, itching, burning, cramps or pain, causing in the person concerned the irresistible urge to move. This disorder occurs most frequently when the person concerned is resting. It is particularly during the night's sleep that this sensory disorder with its attendant kinetic urge leads to restlessness and sleep interruptions. RLS can occur at any age but increases in frequency as persons grow older. It afflicts about 10% of the general population. Because of the nature of the symptoms, RLS is one of the most prevalent causes of sleep disturbances. In 20-40 year-olds, RLS accounts for 5%, in 40-60 year-olds for 20% and in those over 60 years of age for 35% of their sleeping-waking problem. Once the quality of sleep and thus of life of a patient has increasingly deteriorated due to RLS or the patient suffers from daytime somnolence, the need for therapy is indicated. Such need for therapy usually sets in at the age of 40-50 (U.S. Patent Application Publication No. 2004/0048779, paragraphs 0002 to 0005).

[0018] Therapy studies have revealed a diversity of results obtained in monotherapeutic treatments with dopamine agonists, opiates, benzodiazepines, carbamazepine, clonidine or levodopa (L-DOPA) in combination with a dopa decarboxylase inhibitor. The use of L-DOPA for treating RLS has been the subject of a particularly large number of papers. Long-term L-DOPA therapy leads to a clear mitigation of the disorder with an improved quality of sleep and life. The drawback of L-DOPA therapy, however, lies in the fact that in a great many patients its effectiveness tapers off and/or the RLS problem is shifted toward the morning hours (rebound) or the disorder is aggravated with the problem occurring even during the day (augmentation) (U.S. Patent Application Publication No. 2004/0048779, paragraph 0006).

[0019] Administration of rotigotine has been shown to lead to the suppression and reduction of RLS symptoms (U.S. Patent Application Publication No. 2004/0048779, paragraph 0012).

SUMMARY OF THE INVENTION

[0020] Based on the results of human clinical trials involving both healthy subjects and early-stage Parkinson's patients the inventors have found that a transdermal therapeutic system (TTS) comprising a silicone matrix and rotigotine in its free base form produces a rotigotine pharmacokinetic profile with unexpectedly high plasma levels of rotigotine, a controlled release, substantially stable rotigotine blood plasma levels over time, and substantially uniform rotigotine plasma levels when the patch is placed at a variety of skin sites. For example, the inventors have demonstrated that a silicone-based TTS containing rotigotine in the free base form provides mean maximum drug plasma levels in the range of almost 0.5 ng/mL for a 20 cm^2 silicone patch containing 9 mg of rotigotine.

[0021] As such, the invention contemplates a treatment regimen that allows for repeated daily administration that achieves a steady state plasma concentration effective for alleviating symptoms of Parkinson's Disease. In particular, the methods of this invention produce continuous rotigotine plasma levels, which can be a more effective treatment than regimens producing pulsatile plasma levels.

[0022] The invention relates to methods for providing substantially controlled release of rotigotine and for inducing substantially steady-state rotigotine pharmacokinetic profiles over 24 hour period in a human patient in need thereof is provided, wherein the C_{max} of rotigotine is from about 0.14 ng/mL to about 1.54 ng/mL and the AUC_{0-t} is from about 3.3 ng/mL*h to about 32.2 ng/mL*h, said method comprising administering rotigotine to said human patient. In other aspects, the invention relates to methods for providing substantially controlled release of rotigotine and for inducing substantially steady-state rotigotine pharmacokinetic profiles over other and longer time periods, wherein the human patent suffers from Parkinson's Disease, Restless Legs Syndrome or another disease associated with the dopaminergic system. The invention also relates to methods for multiple administrations of rotigotine patches, and to methods for providing substantially controlled release of rotigotine and for inducing substantially steady-state rotigotine pharmacokinetic profiles by placing rotigotine skin patches at various skin sites. The methods of the invention encompass administration of rotigotine in various intervals effective to sustain a C_{max} at a level from about 0.14 ng/mL to about 1.54 ng/mL and the mean area under the curve (AUC_{0-t}) at a level from about 3.3 ng/mL *h to about 32.2 ng/mL *h. The invention also relates to methods that involve rotating the transdermal application site on a daily basis, wherein the pharmacokinetic profiles remain unchanged.

[0023] In another aspect, the invention relates to a controlled release rotigotine formulation for transdermal administration to human patients, comprising from about 4 to about 20 mg rotigotine, where the formulation provides a mean maximum plasma concentration (C_{max}) of

rotigotine from about 0.14 ng/mL to about 1.54 ng/mL and a mean area under the curve up to the last quantifiable concentration (AUC_{0-t}) from about 3.3 ng/mL*h to about 32.2 ng/mL*h.

[0024] In other, preferred aspects of the invention, the C_{max} of rotigotine induced by the formulation is from about 0.20 ng/mL to about 1.30 ng/mL; from about 0.30 ng/mL to about 1.20 ng/mL; from about 0.14 ng/mL to about 0.48 ng/mL; from about 0.37 ng/mL to about 0.75 ng/mL; or from about 0.84 ng/mL to about 1.54 ng/mL. In yet other preferred aspects of the invention, the induced C_{max} is about 0.31 ng/mL ; about 0.56 ng/mL ; or about 1.19 ng/mL.

[0025] In other aspects of the invention, the induced area-under-the-curve of the pharmacokinetic profile over time "t" ("AUC_{0-t}") is from about 4.0 ng/mL*h to about 30.0 ng/mL*h; from about 5.0 ng/mL*h to about 25.0 ng/mL*h; from about 3.3 ng/mL*h to about 8.9 ng/mL*h; from about 7 ng/mL*h to about 15.2 ng/mL*h; or from about 15.2 ng/mL*h to about 32.2 ng/mL*h. In other aspects, the induced AUC_{0-t} is about 6.1 ng/mL*h ; about 11.1 ng/mL*h ; or about 23.7 ng/mL*h.

[0026] In another aspect of the invention, a method for treating Parkinson's Disease in human patient is provided, comprising administering rotigotine which, upon administration, provides a C_{max} of from about 0.14 ng/mL to about 1.54 ng/mL and wherein the AUC_{0-t} is from about 3.3 ng/mL*h to about 32.2 ng/mL*h.

[0027] In another aspect of the invention, a method for treating Restless Legs Syndrome in human patient is provided, comprising administering rotigotine which, upon administration, provides a C_{max} of from about 0.14 ng/mL to about 1.54 ng/mL and wherein the AUC_{0-t} is from about 3.3 ng/mL*h to about 32.2 ng/mL*h.

[0028] In one embodiment, the invention relates to a controlled release rotigotine formulation for transdermal administration to human patients, wherein said formulation gives the same pharmacokinetic profile regardless of where it is applied on the body of said human patient. In a preferred embodiment, the patient is suffering from Parkinson's disease. In another preferred embodiment, the patient is suffering from Restless Legs Syndrome.

DESCRIPTION OF THE FIGURES

Figure 1 - Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 9.0mg rotigotine with Patch A.

Figure 2 - Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 18.0mg rotigotine with 2 x Patch A.

Figure 3 - Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 33.48mg rotigotine (state) with Patch B.

Figure 4 - Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after multiple transdermal administration of 4.5mg rotigotine with Patch C.

Figure 5 - Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after last transdermal administration of 4.5mg rotigotine with Patch C.

Figure 6 - Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 4.5mg rotigotine with Patch D.

Figure 7 - Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 4.5mg rotigotine with Patch C.

Figure 8 - Mean plasma concentrations versus time for each of the six application sites using combined data from Days 27 and 30 (after normalization by body weight and apparent dose).

Figure 9 - Plasma concentration over time for all patch application sites (after normalization by body weight and apparent dose).

Figure 10 - Arithmetic mean and standard deviation of the rotigotine plasma concentrations (ng/mL) during titration and maintenance phase.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. Transdermal Therapeutic Systems

[0029] Transdermal therapeutic systems (TTS) of the present invention may be prepared using methods known in the art or as described in Published U.S. Patent Application Nos. US2003/0026830 and US2003/0027793 and U.S. Patent No. 6,884,434, the disclosure of which as they relate to preparation of TTS's are incorporated by reference herein in their entirety.

[0030] In an embodiment, a TTS of the present invention is reservoir or matrix type transdermal system composed of one or more layers. In a further embodiment the TTS includes a backing layer and a liner layer that is removed prior to use.

[0031] In a preferred embodiment, a TTS of the present invention is a thin, matrix-type transdermal system composed of three layers:

(1) a flexible backing which is preferably siliconised on its inner side and is consisting of an aluminized polyester foil coated with a pigment-layer on the outer side or a transparent polyester film; and

(2) a self-adhesive drug matrix layer comprising of the active component rotigotine, ascorbyl palmitate, dl-alpha tocopherol, silicone adhesive, povidone, and sodium metabisulfite; and

(3) a protective liner, comprising of a transparent fluoropolymer-coated polyester film, which liner is removed prior to application.

[0032] A preferred process for making the TTS is described in U.S. Patent Application Publication No. US 2003/0026830 at paragraphs 38-42 and U.S. Patent Application Publication No. US 2003/0027793 at paragraphs 37-41, which are incorporated herein by this reference.

[0033] A preferred TTS of the present invention may contain from about 4 to about 20 mg of the rotigotine free base. In preferred embodiments, the TTS contains about 4.5 mg of the rotigotine free base, about 9 mg of the rotigotine free base, about 13.5 mg of the rotigotine free base, or about 18 mg of the rotigotine free base. In another preferred embodiment, the TTS contains 5 – 25% (w/w) rotigotine.

[0034] In a preferred embodiment of the present invention, the TTS is in the form of a patch. The release surface area of the patch may be from about 10 cm^2 to about 40 cm^2. In preferred embodiments of the present invention, the release surface area of the patch is about 10 cm^2, about 20 cm^2, about 30 cm^2, or about 40 cm^2.

[0035] A preferred embodiment of the invention utilizes a TTS containing one or more of the following: a pharmaceutically acceptable carrier (e.g., polyvinylpyrrolidone), sodium bisulfite, ascorbyl palmitate, DL-alpha-tocopherol, an amine resistant high tack silicone adhesive (e.g., BIO-PSA® Q7-4301; Dow Corning), and an amine resistant medium tack silicone adhesive (e.g., BIO-PSA® Q7-4201, Dow Corning). For example, a preferred 20 cm^2 patch TTS contains the components in the amounts described in Table 1.

Table 1

Components	Amount (mg)
Rotigotine free base	9.00
Polyvinylpyrrolidone	2.00
Silicone BIO-PSA® Q7-4301	44.47
Silicone BIO-PSA® Q7-4201	44.46
Ascorbyl palmitate	0.02
DL-alpha tocopherol	0.05
Sodium metabisulfite	0.0006

[0036] In a particularly preferred embodiment, the TTS comprises a self-adhesive matrix layer containing the free base of rotigotine in an amount effective for the treatment of the symptoms of Parkinson's Disease or restless legs syndrome (RLS), wherein the matrix is based on a silicone-based polymer adhesive system in which rotigotine free base is dispersed; a backing layer inert to the components of the matrix layer; and a protective foil or sheet covering the matrix layer to be removed prior to use. The TTS may also further comprise inert fillers to improve cohesion, e.g. polyvinylpyrrolidone. The TTS may also further comprise additives that facilitate a homogeneous dispersion of rotigotine particles in the form of hydrophilic polymers (e.g., polyvinylpyrrolidone, a copolymer of vinylpyrrolidone and vinylacetate, and a copolymer of ethylene and vinylacetate).

[0037] When the above-mentioned hydrophilic polymer is polyvinylpyrrolidone, the polyvinylpyrrolidone is present in the active substance-containing matrix layer in the form of insoluble particles at a concentration of 1.5 – 5% (w/w).

[0038] In one preferred embodiment, a TTS of the present invention is used to treat Parkinson's Disease or restless legs syndrome (RLS). As is used herein, the term "treatment" is meant to designate a treatment or alleviation of the symptoms of Parkinson's Disease or RLS, rather than a real causative treatment leading to a complete cure.

II. Rotigotine Pharmacokinetics and the TTS

A. Pharmacokinetics

[0039] In an embodiment of the invention, the C_{max} of rotigotine induced by the formulation is from about 0.20 ng/mL to about 1.30 ng/mL; from about 0.30 ng/mL to about 1.20 ng/mL; from about 0.14 ng/mL to about 0.48 ng/mL; from about 0.37 ng/mL to about 0.75 ng/mL; or from about 0.84 ng/mL to about 1.54 ng/mL. In yet other preferred aspects of the invention, the induced C_{max} is about 0.31 ng/mL ; about 0.56 ng/mL ; or about 1.19 ng/mL.

[0040] In other aspects of the invention, the induced area-under-the-curve of the pharmacokinetic profile over time "t" ("AUC_{0-t}") is from about 4.0 ng/mL*h to about 30.0 ng/mL*h; from about 5.0 ng/mL*h to about 25.0 ng/mL*h; from about 3.3 ng/mL*h to about 8.9 ng/mL*h; from about 7 ng/mL*h to about 15.2 ng/mL*h; or from about 15.2 ng/mL*h to about 32.2 ng/mL*h. In other aspects, the induced AUC_{0-t} is about 6.1 ng/mL*h ; about 11.1 ng/mL*h ; or about 23.7 ng/mL*h.

[0041] In another preferred embodiment, the TTS is used in a method for treating Parkinson's Disease in humans, comprising administering rotigotine which, upon administration, provides a C_{max} of from about 0.14 ng/mL to about 1.54 ng/mL and wherein the AUC_{0-t} is from about 3.3 ng/mL*h to about 32.2 ng/mL*h.

[0042] The invention contemplates a TTS used to administer 0.5 mg to 20 mg rotigotine over a 24 hour period.

[0043] In preferred embodiments, a TTS of the present invention is used to administer 2, 4, 6, or 8 mg rotigotine over a 24 hour period. In certain embodiments, the TTS used to deliver the aforementioned dosages contains, at the time of application, 4.5, 9, 13.5, or 18 mg rotigotine, respectively.

[0044] When applied once daily, a TTS of the present invention produces a sustained and relatively stable rotigotine plasma level. Figures 1-2 show a sustained and relatively stable rotigotine plasma level over a 24 hour period after single administration of a preferred patch (described in Example 1). In animal models of Parkinson's Disease, the presence of stable plasma levels of dopamine agonists such as rotigotine resulted in lower incidence of diskinesias compared to pulsatile plasma levels produced by intermittent administration. Chase, T.N., *Drugs 55 Suppl. 1*: 1 – 9 (1998); Stocchi, F. and Olanow, C.W., *Neurology 62 (1 Suppl. 1)*: S56 – S63 (2004).

[0045] Rotigotine is released at a controlled rate following application of a TTS of the present invention to the skin. Approximately 45% of the rotigotine content of the TTS is released within 24 hours. Steady-state rotigotine plasma concentrations are reached after one to two

days of transdermal administration and are maintained by once daily application of the TTS, where the TTS is worn by the patient for 24 hours. In the clinical trials of rotigotine effectiveness using neupro™, the mean trough plasma concentrations of rotigotine were stable over the six months of maintenance treatment. The bioavailability of rotigotine was similar across all application sites. Figure 9 shows that the AUC_{0-t} and the C_{max}, for example, are comparable whether the TTS of the present invention is administered to the hip, shoulder, upper arm, thigh, abdomen or flank.

[0046] Rotigotine plasma levels have been determined in unconjugated blood samples or conjugated blood samples.

[0047] Exposure to rotigotine from daily application of the TTS of the present invention in healthy subjects and Parkinson's Disease patients exhibited a consistent exposure profile. Repeated daily administration resulted in stable plasma levels. After removal of the TTS, plasma levels decrease with an elimination half-life life of 5 to 7 hours.

[0048] Pharmacokinetic parameters observed after single dose or multiple dose application of a preferred TTS of the present invention to healthy subjects are summarized in Table 2.

Table 2

Dose/24 hours (TTS dimension) (n)	Design	C_{max} [#1]	AUC_{0-t} [#1] (ng/mL*h)	CL [#1] (L/min)
4.5 mg (10 cm^2) (n = 29)	MD [#2]	0.31 ± 0.17	6.1 ± 2.8	8.1 ± 5.3
9 mg (20 cm^2) (n = 13)	SD [#3]	0.56 ± 0.19	11.1 ± 4.1	8.0 ± 2.2
18 mg (2*20 cm^2) (n = 11)	SD [#3]	1.19 ± 0.35	23.7 ± 8.5	7.5 ± 2.0

[#1] Mean ± SD
[#2] Multiple Dose, see example 2
[#3] Single Dose, see example 1
C_{max} is the mean maximum plasma concentration.
AUC_{0-t} is the mean area under the curve until the last quantifiable concentration.
CL is clearance.

B. Preferred Embodiments

[0049] In a preferred embodiment of the present invention, the TTS contains a controlled release rotigotine formulation for transdermal administration to human patients, comprising from about 4 to about 20 mg rotigotine, said formulation resulting in a mean maximum plasma

concentration (C_{max}) of rotigotine from about 0.14 ng/mL to about 1.54 ng/mL and a mean area under the curve up to the last quantifiable concentration (AUC_{0-t}) from about 3.3 ng/mL*h to about 32.2 ng/mL*h.

[0050] In a preferred embodiment of the present invention, the TTS contains a controlled release rotigotine formulation for transdermal administration to human patients, comprising from about 4.5 to about 18 mg rotigotine, said formulation providing a mean maximum plasma concentration (C_{max}) of rotigotine from about 0.14 ng/mL to about 1.54 ng/mL and a mean area under the curve up to the last quantifiable concentration (AUC_{0-t}) from about 3.3 ng/mL*h to about 32.2 ng/mL*h.

[0051] In still another preferred embodiment, the TTS is used in a method for inducing a steady-state rotigotine pharmacokinetic profile over a 24 hour period in a human patient suffering from Parkinson's Disease, wherein the C_{max} of rotigotine is from about 0.14 ng/mL to about 1.54 ng/mL and the AUC_{0-t} is from about 3.3 ng/mL*h to about 32.2 ng/mL*h, said method comprising administering rotigotine to said human patient.

[0052] In an embodiment, the invention relates to a method for treating Parkinson's Disease in a human patient, comprising administering to the patient a rotigotine formulation capable of providing a plasma concentration effective to alleviate the symptoms of Parkinson's Disease, wherein the C_{max} is from about 0.14 ng/mL to about 1.54 ng/mL and wherein the mean area under the curve (AUC_{o-t}) is from about 3.3 ng/mL *h to about 32.3 ng/mL *h. In certain embodiments, the formulation is administered daily in 24 hour intervals.

[0053] In another embodiment, the invention relates to a method for treating Parkinson's Disease in a human patient, comprising administering to the patient a rotigotine formulation capable of maintaining a plasma concentration effective to alleviate the symptoms of Parkinson's Disease, wherein the C_{max} is sustained at a level from about 0.14 ng/mL to about 1.54 ng/mL and wherein the mean area under the curve (AUC_{o-t}) is from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

[0054] In yet another embodiment, the invention relates to a method of treating Parkinson's Disease in a human patient, comprising applying a transdermal therapeutic system (TTS) comprising rotigotine, wherein the TTS is capable of providing a plasma concentration effective to alleviate the symptoms of Parkinson's Disease, wherein the C_{max} is from about 0.14 ng/mL to about 1.54 ng/mL and wherein the mean area under the curve (AUC_{o-t}) is from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

[0055] In a further embodiment, the invention relates to a method of treating Parkinson's Disease in a human patient comprising applying one or more transdermal patches comprising an amount of rotigotine from 4 mg to 20 mg to the human patient; so as to produce in the human patient a mean maximum plasma concentration (C_{max}) of rotigotine effective to alleviate the symptoms of Parkinson's Disease in the human patient, wherein the C_{max} of rotigotine in the patient is sustained at a level from about 0.14 ng/mL to about 1.54 ng/mL and the last quantifiable concentration (AUC_{o-t}) of the rotigotine in the patient is sustained at a level from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

[0056] In a further embodiment, the invention relates to a method of treating Parkinson's Disease in a human patient comprising

a) applying one or more transdermal patches comprising an amount of rotigotine from 4 mg to 20 mg to the human patient;

b) removing the patch or patches of step a) and applying another patch or patches comprising an amount of rotigotine from 4 mg to 20 mg to the human patient at an interval so as to produce in the human patient a mean maximum plasma concentration (C_{max}) of rotigotine effective to alleviate the symptoms of Parkinson's Disease in the human patient; and

c) repeating step b) as required to sustain the C_{max} of rotigotine in the human patient at a level effective to alleviate the symptoms of Parkinson's Disease in the human patient wherein the C_{max} of rotigotine is sustained at a level from about 0.14 ng/mL to about 1.54 ng/mL.

[0057] In a preferred embodiment of the invention, the C_{max} of rotigotine in the human patient is sustained from 3 days to 28 weeks, from 1 to 7 days, from 1 to 6 weeks, for 7 weeks, from 8 to 28 weeks or for 28 weeks.

[0058] In another preferred embodiment of the invention, the patch or patches are removed and another patch or patches are applied daily, twice daily, weekly, twice weekly, monthly or twice monthly.

[0059] In other, preferred aspects of the invention, the C_{max} of rotigotine in the human patient is sustained at a level from about 0.20 ng/mL to about 1.30 ng/mL; from about 0.30 ng/mL to about 1.20 ng/mL; from about 0.14 ng/mL to about 0.48 ng/mL; from about 0.37 ng/mL to about 0.75 ng/mL; or from about 0.84 ng/mL to about 1.54 ng/mL. In yet other preferred aspects of the invention, the induced C_{max} is about 0.31 ng/mL ; about 0.56 ng/mL ; or about 1.19 ng/mL.

[0060] In one embodiment, the invention relates to a controlled release rotigotine formulation for transdermal administration to human patients, wherein said formulation is capable

of providing a plasma concentration effective to alleviate the symptoms of Parkinson's Disease regardless of where it is applied on the body of said human patient. In a preferred embodiment, the patients are suffering from Parkinson's disease. In another preferred embodiment, the patients are suffering from restless legs syndrome. In still another embodiment, the patients are suffering from a disease related to the dopaminergic system.

[0061] In another embodiment, the invention relates to a method for inducing a steady-state rotigotine pharmacokinetic profile over a 24 hour period in a human patient in need thereof comprising administering rotigotine to said human patient, wherein the C_{max} of rotigotine is from about 0.14 ng/mL to about 1.54 ng/mL and the AUC_{0-t} is from about 3.3 ng/mL *h to about 32.2 ng/mL *h, wherein the method gives the same C_{max} and AUC_{0-t} regardless of where the rotigotine is administered to the body of the human patient.

[0062] In another embodiment, the invention relates to a method for treating Parkinson's Disease in a human patient, comprising administering to the patient over a 24 hr period a rotigotine formulation capable of providing a plasma concentration effective to alleviate the symptoms of Parkinson's Disease, wherein the C_{max} is from about 0.14 ng/mL to about 1.54 ng/mL and the AUC_{0-t} is from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

[0063] In another embodiment, the invention relates to a method provides the same plasma concentration effective to alleviate the symptoms of Parkinson' disease regardless of where the rotigotine is administered to the body of the human patient.

[0064] In yet another embodiment, the invention relates to a method of treating Parkinson's Disease in a human patient comprising applying one or more transdermal patches comprising an amount of rotigotine from 4 mg to 20 mg to the patient to provide a plasma concentration effective to alleviate the symptoms of Parkinson's Disease in the human patient, wherein the C_{max} is sustained at a level from about 0.14 ng/mL to about 1.54 ng/mL and the mean area under the curve (AUC_{0-t}) of the rotigotine in the patient is from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

[0065] In an embodiment of the invention, a single daily dose of rotigotine should be initiated and then increased in increments to an effective dose. In another embodiment, the dose is administered with a transdermal therapeutic system (TTS). In yet another embodiment, the TTS is applied once a day. In a further embodiment, the TTS should be applied at the same time every day. In another embodiment, the application site of the TTS should be moved on a daily basis, for example from the right side to the left side and from the upper body to the lower body.

[0066] In certain embodiments, the transdermal system is replaced every 48 hours preferably every 24 hours. The application site does not affect the pharmacokinetic profile. In non-limiting examples the TTS can be applies to the front of the abdomen, thigh, hip, flank,

shoulder or upper arm. Preferably the TTS is moved on a daily basis, for example from the right side to the left side, from the upper body to the lower body. Preferable the TTS is not applied to the same site more than once every 7 days, 10 days, 14 days, 17 days or 21 days.

[0067] The present invention is illustrated by the following examples, without limiting the scope of the invention.

Abbreviations

[0068] As used above, and elsewhere herein, the following terms and abbreviations have the meanings defined below:

AUC_{0-t}: area under the curve from zero up to the last quantifiable concentration.

AUC(0-48): area under the curve from zero up to 48 hours after administration.

AUC_{0-Inf}: area under the curve from zero up to infinity calculated using the area under the curve after the first 24 hours (AUC_{0-24}) and extrapolating to infinity such that $AUC_{0-inf} = AUC_{0-24}$ + plasma concentration at 24 hours/k_{el}.

C_{trough}: measured trough plasma concentration.

CL: total body clearance.

C_{max}: maximum measured plasma concentration

$C_{max,\tau}$: maximum measured plasma concentration during a dose interval ,τ.

C_{min}: minimum measured plasma concentration.

$C_{min,\tau}$: minimum measured plasma concentration during a dose interval τ.

CV: coefficient of variation.

k_{el}: rate constant of elimination.

LLQ: lower limit of quantification.

std: standard deviation

swing: fluctuation of the plasma concentration calculated by $(C_{max} - C_{min}) / (0.5*C_{max} + 0.5*C_{min}) * 100\%$.

t_{lag}: lag time; elapsed time until onset of absorption.

t_{max}: time of C_{max}.

t_{min}: time of C_{min}.

(Site of administration: H = hip, S = shoulder, UA = upper arm, T = thigh, AB = abdomen, F = flank

EXAMPLE 1

Study Design and Subject Population

[0069] A single-center, open-label, single administration, three-way cross-over clinical trial was performed to assess the blood levels and comparative bioavailability of rotigotine from silicone and acrylic transdermal patches. The acrylic transdermal patches were made in accordance with the teachings of WO 99/49852. The silicone transdermal patches were made in accordance with the teachings of U.S. Patent Application Publication No. US 2003/0026830 at paragraphs 38-42, U.S. Patent Application Publication No. US 2003/0027793 at paragraphs 37-41 and U.S. Patent No. 6,884,434, columns 5-6, Example 2 and comprised the following components:

Patch A

Name of Ingredient	mg/20 cm^2 patch
Rotigotine	9.00
Silicone adhesive 4301	44.47
Silicone adhesive 4201	44.46
Providone	2.00
Sodium metabisulfite	0.0009
Ascorbyl palmitate	0.02
Vitamin E (DL-α-tocopherol)	0.05
Scotchpak 1109 (backing film)	20 cm^2

Patch B

Name of Ingredient	mg/20 cm^2 patch
Rotigotine HCl	33.48
Sodium trisilicate	19.2
Oleyl alcohol	12
Vinylacetate-acrylate copolymer	44.26
Eudragit E 100	11.06
Polyester (separator film)	20 cm^2
Silicone adhesive 4301 (overlay)	174.6
Silicone oil Q7 9120 (overlay)	5.4
Hostaphan RN 15 backing film	30 cm^2

[0070] In a first period, a single silicone patch A was administered to each of 14 healthy male subjects (Caucasian race, aged 18 - 50 years) for a period of 24 hours. After a six day wash-out period, the same subjects were in randomized order administered either a single acrylic patch B for 24 hours in the second period followed another six day wash-out period and then administered two silicone patches A for 24 hours in the third period or administered two silicone patches A for 24 hours in the second period followed another six day wash-out period and then administered a single acrylic patch B for 24 hours in the third period. The silicone patches, had a rotigotine content of 9 mg /20 cm^2 and the acrylic patches had a rotigotine content of 33.48 mg /20 cm^2.

[0071] During each study period blood samples for the analysis of rotigotine were taken before patch application and at 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, 15 h, 23 h, 24 h, 25 h, 26 h, 27 h, 28 h, 30 h, 32 h, 36 h, 40 h and 48 h after first patch application.

[0072] To characterize the pharmacokinetics of rotigotine after administration of rotigotine patches in healthy volunteers, the maximum plasma concentration (C_{max}) and the corresponding timepoint (t_{max}) were taken and the data was separated by formulation (and dose). For each sequence of plasma concentrations the AUC was calculated using the trapezoidal rule. $AUC_{(0-t)}$ represents the AUC from patch administration up to the last quantifiable plasma concentration (e.g., if the concentration dropped to below quantifiable levels in less than 48 hours) whereas $AUC_{(0-48)}$ presents the AUC from patch administration to the last sampling point, 48 h after start of administration. The total body clearance was calculated from the individual apparent dose and the corresponding AUC. AUC was the individual area under the concentration time curve extrapolated to infinity: AUC = AUC(0-t) + C(t)/kel, where C(t) is the last quantificable plasma concentration.

Plasma Concentrations of Rotigotine

[0073] Data for the rotigotine plasma concentrations and pharmacokinetic parameters measured during this clinical trial for the silicone patches are provided in Tables 3, 4, 5, and 6. Data for rotigotine plasma concentration for the acrylic patch are provided in Tables 7 and 8. Figures 1 and 2 illustrate the arithmetic mean of rotigotine plasma concentration for single dose administration of the silicone patch. Figure 3 illustrates the arithmetic mean of rotigotine plasma concentration for single dose administration of the acrylic patch.

Table 3: Individual rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 9.0mg rotigotine with Patch A (n.s. = no sample).

subj.	time [h]									
no.	0	1	2	4	6	8	12	15	23	24
1	0	0	0	0	0.0783	0.166	0.297	0.381	0.456	0.406
2	0	0	0	0.119	0.211	0.467	0.5	0.537	0.606	0.459
3	0	0	0	0.0107	0.06	0.162	0.293	0.34	0.367	0.42
4	0	0	0	0.0675	0.462	0.648	0.685	0.831	0.671	0.645
5	0	0	0	0.0717	0.241	0.348	0.496	0.526	0.721	0.612
6	0	0	0	0.0616	0.156	0.334	0.446	0.478	0.586	0.564
7	0	0	0	0.0223	0.0845	0.172	0.239	0.306	0.318	0.319
8	0	0	0	0.017	0.126	0.223	0.278	0.323	0.449	0.441
9	0	0	0.0265	0.156	0.304	0.374	0.461	0.434	0.511	0.466
10	0	0	0	0.0396	0.139	0.202	0.379	0.311	0.235	0.295
11	0	0	0.178	0.862	1.07	1.04	0.945	0.764	0.194	n.s.
12	0	0	0	0	0.0743	0.165	0.352	0.433	0.357	0.379
15	0	0	0.0238	0.376	0.867	0.985	0.849	0.748	0.668	0.647
23	0	0	0.0103	0.4	0.472	0.602	0.492	0.608	0.434	0.493

subj.	time [h]								
no.	25	26	27	28	30	32	36	40	48
1	0.289	0.245	0.228	0.168	0.15	0.103	0.0799	0.0376	0.0179
2	0.325	0.312	0.287	0.235	0.16	0.119	0.053	0.0476	0.0289
3	0.285	0.296	0.182	0.14	0.0798	0.0608	0.04	0.028	0.0137
4	0.489	0.426	0.335	0.277	0.168	0.143	0.0884	0.0521	0.035
5	0.513	0.422	0.382	0.361	0.23	0.149	0.0927	0.0682	0.0535
6	0.382	0.317	0.292	0.275	0.18	0.125	0.0826	0.0664	0.0355
7	0.255	0.229	0.218	0.186	0.132	0.0914	0.0467	0.0281	0.0103
8	0.282	0.281	0.237	0.193	0.145	0.0981	0.0569	0.0386	0.0187
9	0.389	0.297	0.258	0.217	0.129	0.0974	0.0544	0.0257	0.0187
10	0.186	0.162	0.13	0.107	0.0582	0.0386	0.024	0.0163	0
11	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
12	0.306	0.267	0.236	0.178	0.131	0.103	0.0617	0.0288	0.0151
15	0.58	0.516	0.413	0.328	0.166	0.109	0.0752	0.0593	0.0464
23	0.311	0.215	0.177	0.146	0.107	0.0868	0.0379	0.0182	0.0162

Dimension concentration = [ng/ml]

Table 4: Parameters of model independent pharmacokinetics of rotigotine during and after single transdermal administration of 9.0mg rotigotine with Patch A

subj.	C_{max}	t_{max}	AUC(0- 48)	AUC(0-t)	t
1	0.456	23	8.4874	8.4874	48
2	0.606	23	12.5172	12.5172	48
3	0.42	24	7.2922	7.2922	48
4	0.831	15	16.8722	16.8722	48
5	0.721	23	13.9144	13.9144	48
6	0.586	23	11.8375	11.8375	48
7	0.319	24	6.9149	6.9149	48
8	0.449	23	8.3738	8.3738	48
9	0.511	23	11.11405	11.11405	48
10	0.379	12	6.4172	6.352	40
12	0.433	15	8.3696	8.3696	48
15	0.985	8	19.7174	19.7174	48
23	0.608	15	12.79945	12.79945	48
Min	0.319	8	6.4172	6.352	40
Max	0.985	24	19.7174	19.7174	48
Med	0.511	23	11.11405	11.11405	48
Mean	0.562	19.308	11.125	11.12	47.385
SD	0.191	5.498	4.048	4.054	2.219

Dimension: C_{max} [ng/ml] t_{max}, t [h] AUC [ng/ml h]

Table 5: Individual rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 18.0mg rotigotine with 2 x Patch A

subj.	time [h]									
no.	0	1	2	4	6	8	12	15	23	24
1	0	0	0	0.0474	0.228	0.48	0.845	1.11	0.992	0.814
2	0	0	0.0185	0.348	0.976	1.21	1.53	1.35	1.26	1.19
4	0	0	0.0165	0.345	0.955	1.71	1.7	1.56	1.54	1.19
5	0	0	0	0.111	0.413	0.805	1.07	1.19	1.25	1.36
6	0	0	0	0.228	0.54	1.13	1.34	1.55	1.54	1.34
7	0	0	0	0.169	0.438	0.772	0.841	0.819	0.801	0.614
8	0	0	0	0.01	0.0761	0.193	0.31	0.46	0.681	0.501
9	0	0	0.011	0.377	0.806	1.22	1.2	1.33	1.15	1.2
10	0	0	0.0277	0.321	0.565	0.864	0.705	0.678	0.593	0.732
12	0	0	0	0	0.0939	0.17	0.39	0.683	0.655	0.803
23	0	0.0116	0	0.356	1.2	1.28	0.929	1.11	0.866	0.717

subj.	time [h]								
no.	25	26	27	28	30	32	36	40	48
1	0.613	0.567	0.447	0.448	0.289	0.228	0.112	0.0843	0.0432
2	1.09	1.03	0.684	0.494	0.354	0.235	0.127	0.0992	0.0755
4	1.16	0.687	0.558	0.45	0.323	0.205	0.13	0.0847	0.0592
5	1.35	0.89	0.603	0.518	0.358	0.277	0.166	0.113	0.0702
6	1.03	1.05	0.832	0.578	0.304	0.254	0.14	0.091	0.0725
7	0.625	0.616	0.45	0.344	0.208	0.141	0.0809	0.0428	0.0238
8	0.38	0.366	0.266	0.254	0.156	0.112	0.0554	0.0519	0.0304
9	0.808	0.567	0.462	0.402	0.205	0.181	0.112	0.0552	0.0368
10	0.496	0.377	0.285	0.196	0.136	0.0804	0.0407	0.0218	0.0235
12	0.468	0.367	0.325	0.302	0.19	0.155	0.0715	0.04	0.021
23	0.598	0.405	0.334	0.287	0.225	0.165	0.0724	0.0452	0.0419

Dimension concentration = [ng/ml]

Table 6: Parameters of model independent pharmacokinetics of rotigotine during and after single transdermal administration of 18.0mg rotigotine. with 2 x Patch A

subj.	C_{max}	t_{max}	AUC(0- 48)	AUC(0-t)	t
1	1.11	15	21.0189	21.0189	48
2	1.53	12	32.30895	32.30895	48
4	1.71	8	36.01075	36.01075	48
5	1.36	24	27.5278	27.5278	48
6	1.55	15	32.956	32.956	48
7	0.841	12	18.9181	18.9181	48
8	0.681	23	10.6273	10.6273	48
9	1.33	15	28.2519	28.2519	48
10	0.864	8	16.35535	16.35535	48
12	0.803	24	12.6378	12.6378	48
23	1.28	8	24.375	24.375	48
Min	0.681	8	10.6273	10.6273	48
Max	1.71	24	36.01075	36.01075	48
Med	1.28	15	24.375	24.375	48
Mean	1.187	14.909	23.726	23.726	48
SD	0.349	6.252	8.511	8.511	0

Dimension: C_{max} [ng/ml] t_{max}, t [h] AUC [ng/ml h]

Table 7: Individual rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 33.48mg rotigotine with Patch B

subj.	time [h]									
no.	0	1	2	4	6	8	12	15	23	24
1	0	0	0	0	0.0215	0.0612	0.13	0.143	0.158	0.161
2	0	0	0	0.0111	0.0292	0.0491	0.165	0.233	0.281	0.29
4	0	0	0	0.043	0.197	0.326	0.418	0.437	0.348	0.264
5	0	0	0	0	0.0243	0.0617	0.181	0.237	0.274	0.277
6	0	0	0	0.0137	0.0421	0.109	0.221	0.267	0.366	0.341
7	0	0	0	0	0.0185	0.0403	0.0946	0.114	0.114	0.117
8	0	0	0	0	0	0.0139	0.0391	0.0494	0.159	0.193
9	0	0	0	0.0107	0.0241	0.0504	0.0797	0.109	0.137	0.157
10	0	0	0	0.0117	0.0302	0.0821	0.081	0.126	0.096	0.0919
12	0	0	0	0	0	0.0116	0.0299	0.0443	0.112	0.12
15	0	0	0	0.0715	0.143	0.248	0.339	0.298	0.23	0.205
23	0	0	0	0.043	0.0889	0.149	0.142	0.156	0.143	0.147

subj.	time [h]								
no.	25	26	27	28	30	32	36	40	48
1	0.128	0.111	0.11	0.0942	0.0628	0.0459	0.0337	0.0978	0.0126
2	0.192	0.189	0.169	0.163	0.0805	0.059	0.0336	0.0246	0.021
4	0.172	0.145	0.123	0.12	0.07	0.0439	0.0228	0.0162	0.0107
5	0.234	0.184	0.179	0.177	0.0887	0.0691	0.0425	0.022	0.0145
6	0.312	0.287	0.222	0.171	0.105	0.0734	0.0559	0.0296	0.0231
7	0.112	0.108	0.0921	0.083	0.05	0.033	0.017	0.0104	0
8	0.119	0.0849	0.0789	0.0615	0.0462	0.0311	0.0188	0.0103	0.0116
9	0.139	0.0911	0.0842	0.0679	0.0445	0.0421	0.0182	0	0
10	0.0587	0.0662	0.0673	0.0441	0.0232	0.021	0	0	0
12	0.1	0.0757	0.0768	0.0619	0.0553	0.0317	0.0134	0	0
15	0.171	0.152	0.164	0.117	0.0687	0.0445	0.021	0.0171	0.0129
23	0.115	0.104	0.0961	0.0608	0.0296	0.0163	0	0	0

Dimension concentration = [ng/ml]

Table 8: Parameters of model independent pharmacokinetics of rotigotine during and after single transdermal administration of 33.48mg rotigotine with Patch B

subj.	C_{max}	t_{max}	AUC(0- 48)	AUC(0-t)	t
1	0.161	24	3.8657	3.8657	48
2	0.29	24	5.1399	5.1399	48
4	0.437	15	8.2774	8.2774	48
5	0.277	24	5.2879	5.2879	48
6	0.366	23	6.6699	6.6699	48
7	0.117	24	2.512	2.4704	40
8	0.193	24	2.1029	2.1029	48
9	0.157	24	2.577	2.5406	36
10	0.126	15	2.19825	2.15625	32
12	0.12	24	1.61175	1.58495	36
15	0.339	12	6.4101	6.4101	48
23	0.156	15	3.3707	3.3381	32
Min	0.117	12	1.61175	1.58495	32
Max	0.437	24	8.2774	8.2774	48
Med	0.177	24	3.6182	3.6019	48
Mean	0.228	20.667	4.169	4.154	42.667
SD	0.109	4.812	2.154	2.167	6.893

Dimension: C_{max} [ng/ml] t_{max}, t [h] AUC [ng/ml h]

EXAMPLE 2

Study design and Subject Population

[0074] A single-center, open-label, multiple dose clinical trial was performed to assess the pharmacokinetics of a rotigotine transdermal patch during 14 days of once-daily patch administration to 30 healthy male volunteers. The subjects were treated for two days with placebo patches and then either with placebo or rotigotine patches for 14 days (*i.e.*, days 13-16). The silicone transdermal patches were made in accordance with the teachings of U.S. Patent Application Publication No. US 2003/0026830 at paragraphs 38-42, U.S. Patent Application Publication No. US 2003/0027793 at paragraphs 37-41 and U.S. Patent No. 6,884,434, columns 5-6, Example 2 and comprised the following layers and components:

Patch C

Name of Ingredient	mg/10 cm^2 patch
Rotigotine	4.50
Silicone adhesive 4301	22.24
Silicone adhesive 4201	22.23
Providone	1.00
Sodium metabisulfite	0.00045
Ascorbyl palmitate	0.010
Vitamin E (DL-α-tocopherol)	0.025
Scotchpak 1109 (backing film)	10 cm^2

[0075] The silicone patches had a rotigotine content of 4.5mg/10cm^2.

[0076] During the study blood samples for the analysis of rotigotine were taken before patch administration and at 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 316, 320, 324, 336, 337, 338, 339, 340, 342, 344, 350, 360, 372, and 384 hours after first patch administration.

[0077] To characterize the pharmacokinetics of rotigotine after multiple dose administration of rotigotine patches in healthy volunteers the maximum plasma concentration (C_{max}) and the corresponding timepoint (t_{max}) were taken and the data separated by subject. For each time sequence of plasma concentrations the AUC was calculated using the trapezoidal rule. $AUC_{(312-336)}$ represents the AUC within the dose interval of 24 hours under steady state administration.

Plasma Concentrations of Rotigotine

[0078] Data for the rotigotine plasma concentrations and pharmacokinetic parameters measured during this trial are provided in Tables 9 and 10. Figures 4 and 5 illustrate the arithmetic mean of rotigotine plasma concentration during and after multiple patch administration.

Table 9: Individual rotigotine plasma concentrations (in ng/mL) during and after multiple transdermal administration of 4.5mg rotigotine with Patch C.

subj.	time [h]																
no.	0	1	2	4	6	12	24	48	72	96	120	144	168	192	216	240	264
01	0	0	0	.0474	.066	.151	.155	.191	.153	.154	.175	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
02	0	0	0	.111	.269	.383	.36	.335	.324	.414	.297	.333	.234	.36	.264	.269	.279
03	0	0	0	.0577	.13	.184	.206	.237	.2	.241	.204	.233	.27	.212	.196	.208	.241
04	0	0	0	.0404	.0586	.0993	.145	.212	.101	.203	.153	.171	.155	.179	.129	.159	.12
05	0	0	0	.0398	.134	.122	.26	.181	.273	.271	.265	.226	.218	.143	.126	.194	.191
06	0	0	0	0	.0186	.0855	.118	.0998	.0986	.111	.197	.116	.129	.146	.141	.132	.144
07	.0135	0	.0519	.149	.174	.221	.194	.18	.158	.139	.174	.183	.146	.157	.184	.179	.151
08	0	0	0	.0829	.222	.29	.566	.372	.302	.363	.279	.338	.362	.281	.309	.42	.254
09	0	0	0	.0683	.157	.24	.252	.214	.184	.297	.237	.247	.265	.28	.247	.294	.323
10	0	0	0	.0985	.17	.217	.25	.184	.252	.208	.296	.198	.244	.214	.288	.348	.269
11	.0179	0	0	.0135	.0255	.0411	.0437	.0619	.0662	.146	.0586	.0995	.046	.0716	.076	.0705	.132
12	0	0	0	.208	.305	.375	.22	.0421	.338	.175	.214	.387	.256	.152	.386	.123	.11
13	0	0	0	.0128	.0516	.0842	.144	.152	.114	.156	.199	.256	.301	.284	.242	.168	.191
14	0	0	0	.0229	.0662	.113	.0873	.0927	.0821	.0873	.141	.105	.151	.126	.121	.168	.139
15	0	0	.0117	.108	.164	.226	.184	.209	.185	.339	.338	.291	.266	.312	.196	.275	.226
16	0	0	0	0	.0307	.106	.131	.27	.112	.267	.297	.256	.218	.239	.151	.337	.246
17	0	0	0	.0152	.0451	.132	.16	.25	.241	.291	.282	.246	.23	.179	.202	.325	.233
18	0	0	0	.0205	.0729	.147	.135	.163	.129	.202	.187	.208	.19	.192	.211	.166	.168
19	0	0	0	.0153	.0799	.124	.159	.197	.198	.227	.209	.23	.221	.313	.241	.28	.314
20	0	0	0	.043	.118	.154	.141	.199	.213	.241	.279	.22	.254	.229	.246	.248	.485
21	0	0	0	0	0	.0363	.045	.0596	.0512	.0994	.0691	.0918	.0831	.0709	.0765	.0958	.0985
22	0	0	0	.0521	.0827	.123	.127	.169	.199	.256	.247	.222	.182	.253	.304	.289	.291
23	0	0	0	.0591	.0853	.164	.164	.201	.185	.234	.216	.316	.211	.249	.29	.272	.363
24	0	0	.0159	.124	.16	.142	.161	.185	.154	.206	.143	.351	.181	.174	.234	.155	.307
25	0	0	0	.0235	.0641	.125	.13	.211	.204	.234	.18	.252	.233	.252	.24	.228	.269
26	0	0	.0265	.0823	.115	.159	.171	.165	.239	.215	.199	.303	.249	.379	.212	.203	.217
27	0	0	0	.0286	.0618	.0766	.109	.192	.153	.13	.12	.204	.206	.149	.201	.183	.11
28	0	0	0	.0276	.0929	.167	.209	.2	.174	.204	.253	.299	.23	.304	.25	.236	.244
29	0	0	0	.0439	.0887	1.28	.183	.239	.248	.286	.299	.396	.314	.267	.334	.299	.311
30	0	0	0	0	.0169	.0648	.0876	.114	.151	.132	.0937	.155	.129	.172	.107	.113	.142

subj.	time [h]															
no.	288	312	316	320	324	336	337	338	339	340	342	344	350	360	372	384
01	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
02	.307	.268	.291	.385	.357	.298	.284	.218	.207	.16	.111	.0841	.0327	.02	0	0
03	.205	.246	.175	.192	.196	.169	.17	.135	.148	.124	.0615	.0474	.0192	.0109	0	0
04	.15	.274	.152	.233	.164	.13	.134	.118	.094	.0795	.0514	.0279	.0164	0	0	0
05	.363	.407	.355	.311	.335	.262	.184	.146	.139	.0899	.051	.0303	.017	.0116	0	0
06	.205	.148	.12	.172	.168	.19	.147	.136	.145	.113	.0761	.0507	.0299	.0156	0	0
07	.199	.159	.343	.25	.234	.122	.097	.0773	.06	.0537	.0212	.0145	0	0	0	0
08	.386	.399	.441	.479	.306	.405	.249	.194	.114	.128	.0873	.0627	.0303	.0114	0	.0129
09	.292	.398	.254	.342	.356	.334	.233	.177	.158	.139	.0986	.0387	.0369	.0159	.0109	0
10	.335	.287	.408	.513	.521	.296	.276	.232	.194	.159	.0893	.0706	.0402	.034	.0119	.0112
11	.097	.0942	.108	.11	.105	.216	.123	.0932	.084	.0816	.0595	.0453	.0268	.0226	0	.0114
12	.365	.293	.657	.814	.933	.156	.12	.0797	.0847	.0702	.0535	.0425	.0235	.02	0	0
13	.233	.289	.148	.182	.159	.183	.161	.111	.108	.0833	.0647	.0419	.0222	.0133	0	0
14	.15	.126	.0971	.124	.144	.0774	.112	.0809	.0693	.0452	.0257	.022	.0114	0	0	0
15	.227	.274	.244	.244	.272	.229	.228	.189	.187	.13	.0839	.0599	.0293	.0137	0	0
16	.276	.304	.177	.232	.227	.266	.197	.146	.134	.124	.107	.0572	.0386	.016	.0139	0
17	.222	.301	.191	.167	.209	.227	.192	.188	.178	.144	.0967	.0754	.0442	.0284	.0124	.0104
18	.21	.231	.233	.283	.263	.226	.189	.182	.154	.119	.0851	.0553	.0204	.0124	0	0
19	.274	.161	.259	.28	.294	.263	.22	.178	.156	.138	.0952	.0622	.0348	.0328	0	0
20	.176	.184	.305	.396	.389	.268	.227	.162	.122	.0984	.068	.0458	.0158	.0136	0	0
21	.0996	.0992	.0675	.0664	.0756	.0669	.0801	.0733	.0647	.0595	.0392	.0341	.0123	0	0	0

subj.	time [h]															
no.	288	312	316	320	324	336	337	338	339	340	342	344	350	360	372	384
22	.191	.183	.232	.216	.277	.239	.16	.136	.109	.0782	.0539	.0426	.0198	.0134	0	0
23	.271	.173	.129	.128	.146	.169	.139	.109	.105	.117	.0618	.0588	.0312	.0289	.0127	.0155
24	.134	.153	.138	.131	.194	.163	.125	.119	.0806	.0759	.0487	.0402	.0102	0	0	.0131
25	.233	.157	.171	.207	.22	.221	.183	.144	.122	.106	.0683	.0488	.0219	.0111	0	0
26	.114	.221	.309	.223	.253	.169	.183	.128	.0972	.107	.0753	.0569	.0239	.0544	0	0
27	.216	.146	.176	.206	.206	.296	.118	.125	.121	.106	.0487	.0351	.018	0	0	0
28	.247	.266	.373	.394	.495	.233	.203	.201	.192	.137	.105	.0746	.0416	.0136	.0103	0
29	.287	.36	.385	.46	.403	.447	.283	.207	.201	.168	.119	.0889	.0452	.0239	.0143	0
30	.158	.157	.0911	.136	.113	.13	.111	.0887	.0853	.0708	.0461	.0309	.0182	.0118	0	.0385

Dimension concentration [ng/ml]

Table 10: Parameters of model independent pharmacokinetics of rotigotine during and after multiple transdermal administration of 4.5mg rotigotine with Patch C.

subj.	C_{max}	t_{max}	AUC(312- 336)
02	.385	320.0	7.884
03	.196	324.0	4.542
04	.233	320.0	4.18
05	.355	316.0	7.73
06	.19	336.0	3.948
07	.343	316.0	5.294
08	.479	320.0	9.356
09	.356	324.0	8.032
10	.521	324.0	10.202
11	.216	336.0	3.1964
12	.933	324.0	14.87
13	.183	336.0	4.268
14	.144	324.0	2.7528
15	.272	324.0	6.05
16	.266	336.0	5.656
17	.227	336.0	5.068
18	.283	320.0	5.986
19	.294	324.0	6.408
20	.396	320.0	7.892
21	.0756	324.0	1.7402
22	.277	324.0	5.808
23	.169	336.0	3.556
24	.194	324.0	3.912
25	.221	336.0	4.912
26	.309	316.0	5.608
27	.296	336.0	5.244
28	.495	324.0	8.958
29	.46	320.0	10.006
30	.136	320.0	2.9064
Min	.0756	316.0	1.7402
Max	.933	336.0	14.87
Med	.277	324.0	5.608
$\bar{x}$	.307	325.517	6.068
SD	.165	7.044	2.798

Dimension : c-max [ng/ml]; t-max,t [h]; auc [ng/ml h]

EXAMPLE 3

Study Design and Subject Population

[0079] A single-center, open-label, single-dose, randomized two-way cross-over clinical trial was performed to assess bioequivalence of two different rotigotine-containing silicone patches in 30 healthy male subjects (Caucasian, aged 18-50 years). The first silicone transdermal patches (Patch C) were made in accordance with the teachings of U.S. Patent Application Publication No. US 2003/0026830 at paragraphs 38-42, U.S. Patent Application Publication No. US 2003/0027793 at paragraphs 37-41 and U.S. Patent No. 6,884,434, columns 5-6, Example 2 and comprised the following layers and components:

Patch C

Name of Ingredient	mg/10 cm^2 patch
Rotigotine	4.50
Silicone adhesive 4301	22.24
Silicone adhesive 4201	22.23
Providone	1.00
Sodium metabisulfite	0.00045
Ascorbyl palmitate	0.010
Vitamin E (DL-α-tocopherol)	0.025
Scotchpak 1109 (backing film)	10 cm^2

[0080] The second silicone transdermal patches (Patch D) were made in accordance with the teachings of U.S. Patent Application Publication No. US 2003/0026830 at paragraphs 38-42 and U.S. Patent Application Publication No. US 2003/0027793 at paragraphs 37-41and comprised the following layers and components:

Patch D

Name of Ingredient	mg/10 cm^2 patch
Rotigotine	4.50
Silicone adhesive 4301	22.24
Silicone adhesive 4201	22.23
Providone	1.00
Sodium metabisulfite	0.00045
Ascorbyl palmitate	0.010
Vitamin E (DL-α-tocopherol)	0.025
Backing foil PET, siliconized aluminized, color coated	10 cm^2

Ink Bargofor 70135-1-P	As much as needed

[0081] Both patch types contained 4.5 mg rotigotine/10 cm^2. In a first period, patches were administered singly to the subjects for 24 hours. After a washout period of 7 days, the other patch was administered for 24 hours.

[0082] During the study blood samples for the analysis of rotigotine were taken before patch application and at, 1, 2, 4, 6, 8, 10, 12, 15, 23, 24, 25, 26, 27, 28, 30, 36 and 48 hours after first patch application The study was done under in-patient conditions except for the urine collection at 36 – 48 hours and the 48 h blood collection (which were performed on an ambulatory basis).

Plasma Concentrations of Rotigotine

[0083] Data for rotigotine plasma concentrations and pharmacokinetic parameters measured during this clinical are provided in Tables 11, 12, 13, 14, and 15. Figures 6 and 7 illustrate the arithmetic mean of rotigotine plasma concentration for single patch administration. Table 15 summarizes the results of a statistical test to show that the two patch formulations are bioequivalent.

Table 11: Mean rotigotine plasma concentrations (in ng/mL) during and after transdermal administration of 4.5mg rotigotine with Patch D.

Time [h]	Mean	std	Minimum	Maximum	Median	n
0	0.000	0.000	0	0	0	30
1	0.000	0.000	0	0	0	30
2	0.015	0.043	0	177	0	30
4	0.109	0.152	0	622	66.4	30
6	0.137	0.148	0	761	106.8	30
8	0.199	0.150	15	685	170	30
10	0.228	0.169	38	762	185.5	30
12	0.186	0.112	69.2	525	157	30
15	0.194	0.108	48	505	164.5	30
23	0.243	0.163	73.8	766	190.5	30
24	0.221	0.117	95.9	556	197	28
25	0.184	0.081	56.1	378	159	30
26	0.136	0.056	42.3	264	132.5	28
27	0.123	0.059	39.3	259	113	29
28	0.101	0.046	23.1	207	94.35	30
30	0.076	0.040	31.3	200	62.85	30
36	0.032	0.015	10.3	61.4	30.65	30
48	0.009	0.009	0	28.3	11	30

Table 12: Mean rotigotine plasma concentrations (in ng/mL) during and after transdermal administration of 4.5mg rotigotine with Patch C

Time [h]	Mean	std	Minimum	Maximum	Median	n
0	0.000	0.000	0	0	0	30
1	0.000	0.000	0	0	0	30
2	0.010	0.032	0	159	0	30
4	0.080	0.109	0	448	34.55	30
6	0.103	0.099	0	457	65.75	30
8	0.150	0.109	20.1	453	121	30
10	0.191	0.117	23	520	151	30
12	0.195	0.118	35.2	511	150.5	30
15	0.232	0.161	74.9	737	182	30
23	0.240	0.106	98.1	589	243	29
24	0.208	0.101	60.2	505	186.5	30
25	0.193	0.093	48	508	177	30
26	0.159	0.082	66.2	371	149	29
27	0.131	0.063	65.1	307	120	29
28	0.099	0.035	29.2	179	100	30
30	0.074	0.034	26.6	156	70.6	29
36	0.034	0.014	0	59.2	32.5	30
48	0.010	0.012	0	33.6	5.2	30

Table 13: Parameters of model independent pharmacokinetics of rotigotine under administration of 4.5mg rotigotine with Patch D

Parameter	N	Mean	Std	Minimum	Maximum	%CV
AUC(0-tz)	27	5646.9	3031.1	2083.9	13379	53.7
AUC(0-inf)	23	5736.1	2975.7	2251.9	13589	51.9
Cmax	27	323.2	180.8	109	766	56.0
Tmax	27	17.1	6.8	4	27	39.5
k	23	0.1216	0.0383	0.0575	0.2083	31.5
t1/2	23	6.2856	2.0848	3.3275	12.058	33.2

Table 14: Parameters of model independent pharmacokinetics of rotigotine under administration of 4.5mg rotigotine with Patch C

Parameter	N	Mean	Std	Minimum	Maximum	%CV
AUC(0-tz)	30	5307.2	2571.4	2134.3	12583	48.5
AUC(0-inf)	23	5734.7	2553.8	2355.9	13070	44.5
Cmax	30	307.6	152.3	98.1	737	49.5
Tmax	30	17.5	6.5	4	26	37.3
k	23	0.1113	0.0500	0.0646	0.2598	44.9
t1/2	23	7.1416	2.3062	2.6684	10.729	32.3

Table 15: Results of relative bioavailability for rotigoine after administration of Patches C and D

Parameter	$AUC_{(0-t)}$ (n=27)	$AUC_{(0-t)}$ (n=30)	AUC_{0-inf}	C_{max}	$T_{1/2}$	t_{max}
Unit	h*ng/ml	h*ng/ml	h*ng/ml	ng/ml	h	h
Mean* test	5.0117	4.7526	4.9491	0.2841	6.0598	15.0
Mean* reference	4.8262	4.7863	5.2203	0.2766	6.5673	15.0
Difference	0.0377	-0.007	-0.053	0.0267	-0.08	.
SE of Difference	0.0567	0.0602	0.0722	0.0836	0.1093	.
ratio	103.85%	99.30%	94.81%	102.70%	92.27%	96.67%
90% CI lower limit	94.26%	89.63%	83.52%	89.04%	76.18%	83.33%
90% CI upper limit	114.39%	110.00%	107.60%	118.46%	111.76%	113.34%

* = least square means, SE = standard error, CI = confidence interval,

Difference = difference on log-scale

EXAMPLE 4

Study Design and Subject Population

[0084] An open-label, multi-site, randomized trial with daily doses of rotigotine patch applied to the skin of 70 subjects was performed to evaluate the safety, tolerability, and effectiveness of placing the patch on different body sites. The study also evaluated electrocardiographic effects of patch-administered rotigotine. Each day, a fresh patch was placed on a new skin site (abdomen, flank, upper arm, shoulder, thigh, hip) in a rotating order. The silicone transdermal patches were made in accordance with the teachings of U.S. Patent Application Publication No. US 2003/0026830 at paragraphs 38-42, U.S. Patent Application Publication No. US 2003/0027793 at paragraphs 37-41 and U.S. Patent No. 6,884,434, columns 5-6, Example 2 and comprised the following layers and components:

Patches D, E and F

Name of Ingredient	Patch D (mg/10 cm^2 patch)	Patch E (mg/20 cm^2 patch)	Patch F (mg/30 cm^2 patch)
Rotigotine	4.50	9.00	13.50
Silicone adhesive 4301	22.24	44.47	66.71
Silicone adhesive 4201	22.23	44.46	66.70
Providone	1.00	2.00	3.00
Sodium metabisulfite	0.00045	0.0009	0.00135
Ascorbyl palmitate	0.010	0.02	0.03
Vitamin E (DL-α-tocopherol)	0.025	0.05	0.075
Backing foil PET, siliconized aluminized, color coated	10 cm^2	20 cm^2	30 cm^2
Ink Bargofor 70135-1-P	As much as needed	As much as needed	As much as needed

[0085] Rotigotine doses included 4.5mg/day (Patch D), 9.0mg/day (Patch E), 13.5mg/day (Patch F), and 18.0mg/day (2 x Patch E). The trial consisted of an Eligibility Assessment (EA), a 24-day Titration Phase (4.5 to 18.0mg/day doses; incremental increases of 4.5mg/day every 6 days), a 6-day Maintenance Phase (18.0mg/day dose), a 6-day De-escalation Phase (13.5/9.0/4.5mg/day decreasing dose every 2 days), and a Safety Follow-Up visit 2 days following the last dose. A total of 70 subjects were enrolled and randomized; 63 subjects were analyzed for the primary pharmacokinetic (PK) variables and 58 subjects were analyzed for the primary pharmacodynamic variables.

[0086] The objectives of this trial included the following: 1) to characterize the pharmacokinetic profile of rotigotine during 24 hour intervals where the skin site of patch application was rotated in

subjects with early-stage Parkinson's disease, 2) to investigate the electrocardiographic effects of rotigotine over a 24 hour period under maximal anticipated therapeutic exposure in subjects with early-stage Parkinson's disease, and 3) to investigate the safety and local tolerability of a rotigotine transdermal patch under maximal anticipated therapeutic exposure.

[0087] The study used 10 cm^2, 20 cm^2, and 30 cm^2 rotigotine transdermal patches, which correspond to 4.5mg, 9.0mg, and 13.5mg rotigotine, respectively. The silicone transdermal patches were made in accordance with the teachings of U.S. Patent Application Publication No. US 2003/0026830 at paragraphs 38-42 and U.S. Patent Application Publication No. US 2003/0027793 at paragraphs 37-41 comprised the following layers and components as disclosed above

[0088] The 18.0mg/day dose used 2x20 cm^2 patches. Initial doses were 4.5mg/day with weekly increases of 4.5mg/day to a maximum target dose of 18.0mg/day.

[0089] Blood samples were collected before patch administration and on the days and at the times indicated in Table 16.

Plasma Concentrations of Rotigotine

[0090] Mean plasma concentrations versus time for each of the six application sites using combined data from Days 27 and 30 are shown in the Figure 8.

[0091] Mean plasma concentrations of unconjugated rotigotine were similar between the six application sites. Starting with a plasma concentration at Time 0 (prior to patch removal, C_{trough}) of about 1ng/mL, the concentration decreased within 2 hours by about 0.2ng/mL, followed by an increase back up to the level of the trough plasma concentration. Figure 9 illustrates a plasma concentration over time for all patch application sites.

[0092] Table 16 reports the result of descriptive statistics of plasma concentrations for unconjugated rotigotine separated by the day of administration, the time of sampling after actual administration and the site of patch administration.

Table 16: Descriptive statistics of parameters of rotigotine plasma concentrations (ng/mL) under multiple dose in patients with early-stage Parkinson's disease

Application Site = Hip

Day	Time	n	# Obs. >LOQ	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 25	0H	10	10	0.9598	0.89990	93.8	0.7010	2.20222	0.5265	0.271	2.980
	4H	10	10	0.8993	0.67741	75.3	0.6929	2.16680	0.8040	0.256	2.400
	8H	10	10	0.8447	0.78229	92.6	0.5629	2.78343	0.6550	0.114	2.750
	12H	10	10	0.9776	0.79679	81.5	0.6434	2.94450	0.7255	0.094	2.330
Day 26	0H	11	11	0.7716	0.39609	51.3	0.6542	1.93335	0.7250	0.187	1.260
	4H	11	11	0.5491	0.27813	50.7	0.4660	1.94460	0.5250	0.111	0.912
	8H	11	11	0.8153	0.44074	54.1	0.6802	1.98291	0.7620	0.230	1.370
	12H	11	11	0.9108	0.62860	69.0	0.6841	2.43929	0.9420	0.102	2.300
Day 27	0H	10	10	1.3040	1.11784	85.7	1.0111	2.05974	0.8805	0.375	4.150
	1H	10	10	1.2353	1.05886	85.7	0.9845	1.92688	0.9300	0.450	3.980
	2H	10	10	0.9798	0.95288	97.3	0.7477	2.03439	0.7055	0.292	3.550
	4H	10	10	1.0117	1.26502	125.0	0.6774	2.27514	0.5055	0.314	4.440
	5H	10	10	0.8224	0.62891	76.5	0.6431	2.09471	0.6425	0.232	1.970
	6H	10	10	0.7661	0.45889	59.9	0.6546	1.80767	0.5935	0.283	1.560
	7H	10	10	0.8542	0.45527	53.3	0.7356	1.85188	0.7095	0.203	1.730
	8H	10	10	0.8676	0.43667	50.3	0.7580	1.78669	0.7310	0.236	1.520
	10H	10	10	0.9860	0.47824	48.5	0.8971	1.57901	0.8460	0.371	2.130
	12H	10	10	1.0611	0.55365	52.2	0.9429	1.67691	0.8825	0.380	2.280
	14H	10	10	1.0745	0.55728	51.9	0.9609	1.63250	0.9115	0.485	2.080
	16H	10	10	1.3677	0.79763	58.3	1.2073	1.65233	1.0500	0.634	3.090
	18H	10	10	1.1769	0.54621	46.4	1.0728	1.57672	0.9900	0.457	2.140
	20H	10	10	1.2121	0.51482	42.5	1.1143	1.54847	1.0650	0.593	1.970
	22H	10	10	0.9248	0.45066	48.7	0.8350	1.61184	0.8890	0.379	1.920
	23.5H	10	10	0.9600	0.38736	40.4	0.8745	1.64926	0.9570	0.261	1.750
Day 28	4H	11	11	0.7955	0.46452	58.4	0.6786	1.82902	0.5510	0.218	1.570
	8H	11	11	1.1237	0.75207	66.9	0.8577	2.34277	1.0500	0.178	2.300
	12H	11	11	1.0759	0.65385	60.8	0.8227	2.44476	1.0000	0.158	2.130
Day 29	0H	11	11	0.6160	0.28338	46.0	0.5494	1.69457	0.6300	0.209	1.070
	4H	11	11	0.4802	0.28770	59.9	0.4018	1.91554	0.3910	0.131	0.974
	8H	11	11	0.5221	0.26648	51.0	0.4468	1.88281	0.6020	0.133	0.900
	12H	11	11	0.5715	0.29201	51.1	0.5056	1.70189	0.4600	0.180	1.140
Day 30	0H	10	10	1.0048	0.46928	46.7	0.9083	1.61927	0.8680	0.398	1.930
	1H	10	10	0.8518	0.36378	42.7	0.7819	1.56060	0.7840	0.393	1.500
	2H	10	10	0.6981	0.24795	35.5	0.6594	1.42980	0.6430	0.397	1.100
	4H	10	10	0.7967	0.68299	85.7	0.6487	1.85828	0.5950	0.236	2.670
	5H	10	10	0.8458	0.63315	74.9	0.6787	2.01882	0.7460	0.194	2.420
	6H	10	10	1.0816	1.52030	140.6	0.6542	2.61354	0.5810	0.140	5.310

	7H	10	10	0.7566	0.47940	63.4	0.6270	1.94917	0.6825	0.217	1.800
	8H	10	10	0.9441	0.99194	105.1	0.6780	2.25518	0.7225	0.214	3.640
	10H	10	10	0.7786	0.56988	73.2	0.6330	1.96963	0.6990	0.235	2.220
	12H	10	10	0.9966	0.64950	65.2	0.8291	1.91705	0.8425	0.317	2.510
	14H	10	10	0.8877	0.48873	55.1	0.7835	1.67757	0.7380	0.428	1.860
	16H	10	10	1.2098	0.66582	55.0	1.0564	1.74629	1.2200	0.424	2.670
	18H	10	10	1.2131	0.63776	52.6	1.0663	1.71951	1.0250	0.473	2.220
	20H	10	10	1.2665	0.70594	55.7	1.1060	1.72835	1.0255	0.504	2.600
	22H	10	10	1.0856	0.71368	65.7	0.9142	1.84220	0.9330	0.380	2.770
	23.5H	10	10	0.8204	0.34090	41.6	0.7585	1.51856	0.6915	0.461	1.350
Days											
27 & 30	0H	20	20	1.1544	0.84839	73.5	0.9583	1.82270	0.8730	0.375	4.150
Combined											
	1H	20	20	1.0436	0.79528	76.2	0.8774	1.74752	0.8405	0.393	3.980
	2H	20	20	0.8390	0.69289	82.6	0.7021	1.73502	0.6575	0.292	3.550
	4H	20	20	0.9042	0.99557	110.1	0.6629	2.03165	0.5520	0.236	4.440
	5H	20	20	0.8341	0.61432	73.7	0.6607	2.01882	0.6425	0.194	2.420
	6H	20	20	0.9239	1.10489	119.6	0.6544	2.17423	0.5905	0.140	5.310
	7H	20	20	0.8054	0.45777	56.8	0.6791	1.87859	0.6980	0.203	1.800
	8H	20	20	0.9059	0.74695	82.5	0.7169	1.99371	0.7225	0.214	3.640
	10H	20	20	0.8823	0.52297	59.3	0.7536	1.80455	0.7605	0.235	2.220
	12H	20	20	1.0289	0.58831	57.2	0.8842	1.77857	0.8675	0.317	2.510
	14H	20	20	0.9811	0.51907	52.9	0.8677	1.65125	0.8370	0.428	2.080
	16H	20	20	1.2888	0.71967	55.8	1.1294	1.68360	1.1500	0.424	3.090
	18H	20	20	1.1950	0.57821	48.4	1.0695	1.62781	1.0250	0.457	2.220
	20H	20	20	1.2393	0.60198	48.6	1.1101	1.61944	1.0650	0.504	2.600
	22H	20	20	1.0052	0.58675	58.4	0.8737	1.70855	0.9280	0.379	2.770
	23.5H	20	20	0.8902	0.36229	40.7	0.8144	1.57540	0.8700	0.261	1.750

Application Site = Shoulder

Day	Time	n	# Obs. >LOQ	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 25	0H	11	11	0.8450	0.39342	46.6	0.7595	1.66491	0.7700	0.243	1.720
	4H	11	11	1.4656	1.18532	80.9	1.0877	2.29840	1.1300	0.276	4.130
	8H	11	11	1.5562	0.89190	57.3	1.2839	2.01651	1.2700	0.390	2.750
	12H	11	11	1.4674	0.87603	59.7	1.2450	1.84120	1.4900	0.534	3.390
Day 26	0H	11	11	0.9283	0.80108	86.3	0.7068	2.15694	0.7510	0.170	3.020
	4H	11	11	0.8209	0.43510	53.0	0.7038	1.85972	0.9000	0.212	1.600
	8H	11	11	1.0675	0.51786	48.5	0.9399	1.74736	1.1800	0.338	2.020
	12H	11	11	1.1026	0.41510	37.6	1.0094	1.61600	1.2600	0.373	1.700
Day 27	0H	11	11	0.7905	0.58843	74.4	0.6131	2.13333	0.5090	0.188	1.880
	1H	11	11	0.7317	0.46938	64.1	0.6025	1.93539	0.6100	0.239	1.470
	2H	11	11	0.7235	0.38012	52.5	0.6190	1.86084	0.6960	0.223	1.360
	4H	11	11	0.7431	0.44194	59.5	0.6375	1.78507	0.6880	0.283	1.700
	5H	11	11	0.7521	0.56646	75.3	0.6188	1.86218	0.5000	0.293	2.250
	6H	11	11	0.7916	0.63449	80.1	0.6556	1.80693	0.6020	0.287	2.580
	7H	11	11	0.7798	0.44581	57.2	0.6828	1.71130	0.6450	0.258	1.830
	8H	11	11	0.8102	0.59484	73.4	0.6695	1.86679	0.5890	0.253	2.370
	10H	11	11	0.8745	0.42362	48.4	0.7815	1.67369	0.8150	0.290	1.790
	12H	11	11	0.8646	0.43447	50.2	0.7759	1.63179	0.7820	0.339	1.810
	14H	10	10	0.9155	0.37149	40.6	0.8388	1.58945	0.9210	0.357	1.530
	16H	11	11	1.0633	0.57402	54.0	0.9311	1.72241	0.8600	0.412	2.250
	18H	11	11	1.1540	0.58214	50.4	1.0212	1.69632	1.0400	0.431	2.230
	20H	11	11	1.0924	0.45924	42.0	0.9953	1.61217	1.0400	0.372	2.000
	22H	11	11	0.9357	0.41007	43.8	0.8398	1.68826	0.9560	0.289	1.670
	23.5 H	11	11	0.9075	0.52690	58.1	0.7901	1.71665	0.7130	0.387	1.980
Day 28	4H	9	9	1.0613	0.84706	79.8	0.8260	2.08735	0.6080	0.323	2.940
	8H	9	9	1.1016	1.07009	97.1	0.7720	2.46350	0.8690	0.199	3.710
	12H	9	9	1.0689	0.84181	78.8	0.8423	2.10124	0.9110	0.214	3.100
Day 29	0H	10	10	0.8564	0.37266	43.5	0.7862	1.55758	0.8040	0.347	1.650
	4H	10	10	1.0285	0.50781	49.4	0.8838	1.89291	0.9695	0.238	1.640
	8H	10	10	1.1192	0.82177	73.4	0.8413	2.34757	0.8730	0.163	2.560
	12H	10	10	1.0289	0.81504	79.2	0.7421	2.45889	0.7160	0.163	2.620
Day 30	0H	11	11	0.6888	0.32132	46.6	0.6271	1.57060	0.6710	0.316	1.330
	1H	11	11	0.4812	0.17361	36.1	0.4525	1.45073	0.4390	0.239	0.745
	2H	11	11	0.6484	0.31245	48.2	0.5870	1.59214	0.6530	0.334	1.360
	4H	11	11	1.0701	0.65380	61.1	0.9207	1.77194	0.9420	0.380	2.720
	5H	11	11	1.1798	0.86047	72.9	0.9713	1.88398	0.9560	0.360	3.330
	6H	11	11	0.9113	0.38029	41.7	0.8369	1.56205	0.8190	0.364	1.530
	7H	11	11	1.0807	0.45844	42.4	0.9932	1.55158	1.0800	0.438	1.870
	8H	11	11	1.2537	0.84729	67.6	1.0561	1.82857	1.0200	0.372	3.410

	10H	11	11	1.1660	0.55622	47.7	1.0307	1.73365	1.0800	0.369	1.980
	12H	11	11	1.1693	0.54122	46.3	1.0404	1.70227	1.0500	0.401	1.890
	14H	11	11	1.2580	0.58500	46.5	1.1460	1.57295	1.2100	0.580	2.590
	16H	11	11	1.2787	0.66304	51.9	1.1479	1.60896	1.0600	0.600	2.530
	18H	11	11	1.3215	0.77932	59.0	1.1604	1.67705	1.1700	0.577	3.250
	20H	11	11	1.3956	1.19600	85.7	1.1356	1.84877	1.0400	0.427	4.810
	22H	10	10	0.9039	0.43904	48.6	0.8153	1.61217	0.7335	0.398	1.770
	23.5 H	11	11	1.0242	0.75976	74.2	0.8511	1.82764	0.8480	0.405	3.010
Days											
27 & 30 Combined	0H	22	22	0.7397	0.46557	62.9	0.6201	1.83811	0.5915	0.188	1.880
	1H	22	22	0.6065	0.36838	60.7	0.5222	1.72140	0.4560	0.239	1.470
	2H	22	22	0.6859	0.34171	49.8	0.6028	1.70931	0.6910	0.223	1.360
	4H	22	22	0.9066	0.56971	62.8	0.7661	1.80861	0.7855	0.283	2.720
	5H	22	22	0.9660	0.74384	77.0	0.7753	1.92416	0.8045	0.293	3.330
	6H	22	22	0.8515	0.51412	60.4	0.7407	1.69270	0.7555	0.287	2.580
	7H	22	22	0.9303	0.46737	50.2	0.8235	1.67509	0.7655	0.258	1.870
	8H	22	22	1.0320	0.74958	72.6	0.8409	1.90210	0.9045	0.253	3.410
	10H	22	22	1.0203	0.50500	49.5	0.8975	1.71434	0.9450	0.290	1.980
	12H	22	22	1.0170	0.50366	49.5	0.8985	1.68374	0.8870	0.339	1.890
	14H	21	21	1.0949	0.51375	46.9	0.9878	1.60647	1.0700	0.357	2.590
	16H	22	22	1.1710	0.61515	52.5	1.0338	1.66506	1.0170	0.412	2.530
	18H	22	22	1.2378	0.67671	54.7	1.0886	1.67256	1.1350	0.431	3.250
	20H	22	22	1.2440	0.89759	72.2	1.0632	1.71821	1.0400	0.372	4.810
	22H	21	21	0.9206	0.41362	44.9	0.8280	1.63214	0.8480	0.289	1.770
	23.5 H	22	22	0.9659	0.64081	66.3	0.8201	1.75077	0.7995	0.387	3.010

Application Site = Upper Arm

Day	Time	n	# Obs. >LOQ	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 25	0H	10	10	0.8531	0.49953	58.6	0.7157	1.93040	0.7455	0.219	1.770
	4H	10	10	0.6055	0.25103	41.5	0.5603	1.51365	0.5080	0.366	1.000
	8H	10	10	0.7649	0.36745	48.0	0.6892	1.61891	0.6225	0.354	1.420
	12H	10	10	0.9058	0.38785	42.8	0.8191	1.65583	0.8865	0.283	1.540
Day 26	0H	9	9	0.6452	0.26690	41.4	0.5823	1.69184	0.6370	0.192	1.080
	4H	9	9	0.9841	1.16480	118.4	0.6514	2.38356	0.4370	0.290	3.860
	8H	9	9	0.8018	0.58759	73.3	0.6614	1.88172	0.6230	0.292	2.170
	12H	9	9	0.9626	0.60654	63.0	0.8223	1.78312	0.6170	0.413	2.170
Day 27	0H	10	10	1.1664	0.63917	54.8	0.8981	2.62949	1.0750	0.076	2.060
	1H	10	10	0.7850	0.39998	51.0	0.6288	2.42290	0.7060	0.062	1.400
	2H	10	10	0.7760	0.36374	46.9	0.6493	2.16745	0.6835	0.086	1.360

	4H	10	10	0.8503	0.46010	54.1	0.7529	1.67989	0.8085	0.358	1.920
	5H	10	10	1.0106	0.65776	65.1	0.8303	1.95398	0.8270	0.348	2.120
	6H	10	10	0.9577	0.62292	65.0	0.6714	3.17479	0.9535	0.036	2.160
	7H	10	10	0.8950	0.53831	60.1	0.6804	2.57511	0.9335	0.071	1.840
	8H	10	10	0.9987	0.55599	55.7	0.8537	1.84479	0.8595	0.383	2.030
	10H	10	10	0.9798	0.51868	52.9	0.8616	1.71881	0.8135	0.365	1.930
	12H	10	10	1.1466	0.63722	55.6	0.9701	1.92584	1.0255	0.253	2.290
	14H	10	10	1.0699	0.58804	55.0	0.8976	1.97808	0.9335	0.213	2.020
	16H	10	10	1.1540	0.58531	50.7	0.9705	2.03045	1.1030	0.187	1.910
	18H	10	10	1.1039	0.60875	55.1	0.9215	2.02065	0.9330	0.194	2.030
	20H	10	10	1.1564	0.75476	65.3	0.9511	1.99892	0.9700	0.228	2.870
	22H	10	10	1.0020	0.62301	62.2	0.8046	2.13992	0.8670	0.190	2.160
	23.5H	10	10	0.9361	0.55459	59.2	0.7423	2.26567	0.9385	0.129	1.880
Day 28	4H	12	12	0.7681	0.51159	66.6	0.6211	1.99127	0.5480	0.251	1.720
	8H	12	12	1.0700	0.66177	61.8	0.8703	2.08162	1.0000	0.178	2.650
	12H	12	12	0.9082	0.46115	50.8	0.7892	1.79669	0.9415	0.249	1.740
Day 29	0H	11	11	1.0746	0.72989	67.9	0.8627	2.10510	0.9570	0.180	2.870
	4H	11	11	0.8639	0.70262	81.3	0.6623	2.15445	0.6130	0.192	2.650
	8H	11	11	1.1498	0.67779	58.9	0.9496	1.99607	1.1600	0.306	2.470
	12H	11	11	1.2128	0.71743	59.2	1.0161	1.91241	1.1000	0.377	2.490
Day 30	0H	11	11	0.7028	0.23782	33.8	0.6599	1.47979	0.6920	0.314	0.981
	1H	11	11	0.6353	0.31713	49.9	0.5665	1.65855	0.5710	0.269	1.230
	2H	11	11	0.5860	0.16988	29.0	0.5653	1.32079	0.5710	0.375	0.945
	4H	11	11	0.6831	0.30322	44.4	0.6218	1.59139	0.6410	0.278	1.260
	5H	11	11	0.7822	0.38194	48.8	0.6938	1.69794	0.8190	0.314	1.440
	6H	11	11	0.8920	0.45884	51.4	0.7891	1.69564	0.9590	0.381	1.910
	7H	11	11	0.7893	0.37701	47.8	0.7130	1.61065	0.8100	0.358	1.650
	8H	11	11	0.9771	0.39344	40.3	0.9046	1.52119	0.9690	0.449	1.770
	10H	11	11	1.0650	0.63744	59.9	0.9417	1.63598	0.9940	0.562	2.760
	12H	11	11	1.1607	0.69159	59.6	1.0052	1.74277	1.0600	0.475	2.830
	14H	11	11	1.0294	0.37927	36.8	0.9606	1.49647	1.0400	0.488	1.590
	16H	11	11	0.9613	0.45864	47.7	0.8572	1.68573	0.9020	0.312	1.720
	18H	11	11	1.1474	0.46970	40.9	1.0444	1.62876	1.2400	0.351	1.990
	20H	11	11	1.1207	0.59545	53.1	0.9702	1.80101	1.1300	0.354	2.230
	22H	11	11	1.0576	0.41511	39.2	0.9806	1.52585	0.9800	0.415	1.850
	23.5H	11	11	0.9245	0.41698	45.1	0.8333	1.64525	0.8990	0.347	1.670
Days 27 & 30 Combined	0H	21	21	0.9236	0.51808	56.1	0.7642	2.05994	0.8560	0.076	2.060
	1H	21	21	0.7066	0.35798	50.7	0.5954	2.00405	0.6330	0.062	1.400
	2H	21	21	0.6765	0.28882	42.7	0.6038	1.74974	0.6510	0.086	1.360
	4H	21	21	0.7627	0.38543	50.5	0.6811	1.62982	0.7560	0.278	1.920
	5H	21	21	0.8910	0.53037	59.5	0.7557	1.80767	0.8190	0.314	2.120
	6H	21	21	0.9233	0.53011	57.4	0.7307	2.37307	0.9590	0.036	2.160

	7H	21	21	0.8396	0.45210	53.8	0.6973	2.05213	0.8830	0.071	1.840
	8H	21	21	0.9874	0.46543	47.1	0.8800	1.66122	0.9540	0.383	2.030
	10H	21	21	1.0244	0.57108	55.7	0.9026	1.65733	0.8810	0.365	2.760
	12H	21	21	1.1540	0.64955	56.3	0.9884	1.80366	1.0600	0.253	2.830
	14H	21	21	1.0487	0.47745	45.5	0.9301	1.71638	1.0400	0.213	2.020
	16H	21	21	1.0530	0.51872	49.3	0.9094	1.83140	0.9160	0.187	1.910
	18H	21	21	1.1267	0.52684	46.8	0.9840	1.80039	1.1600	0.194	2.030
	20H	21	21	1.1377	0.65876	57.9	0.9610	1.86589	1.0600	0.228	2.870
	22H	21	21	1.0311	0.51150	49.6	0.8924	1.82207	0.9360	0.190	2.160
	23.5H	21	21	0.9300	0.47474	51.0	0.7887	1.92430	0.8990	0.129	1.880

Application Site = Thigh

Day	Time	n	# Obs. >LOQ	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 25	0H	11	11	0.5459	0.31177	57.1	0.4575	1.99998	0.5360	0.087	1.300
	4H	11	11	0.3757	0.18016	47.9	0.3262	1.89010	0.3440	0.062	0.709
	8H	11	11	0.4448	0.25511	57.4	0.3661	2.04796	0.4200	0.087	0.864
	12H	11	11	0.5095	0.30534	59.9	0.4246	1.96224	0.4230	0.105	1.160
Day 26	0H	11	11	0.8664	0.48505	56.0	0.7679	1.64271	0.6140	0.398	1.950
	4H	11	11	0.5822	0.24421	41.9	0.5363	1.53465	0.4920	0.299	0.961
	8H	11	11	0.8017	0.50124	62.5	0.6800	1.81246	0.5910	0.280	1.850
	12H	11	11	0.8817	0.32211	36.5	0.8316	1.43050	0.8790	0.466	1.550
Day 27	0H	9	9	0.7659	0.22662	29.6	0.7316	1.39657	0.8240	0.429	1.010
	1H	9	9	0.6961	0.22690	32.6	0.6580	1.45179	0.7110	0.337	0.998
	2H	9	9	0.6704	0.22674	33.8	0.6336	1.44547	0.6660	0.326	1.040
	4H	9	9	0.7407	0.55140	74.4	0.6006	1.95373	0.5670	0.234	1.970
	5H	9	9	0.6593	0.40489	61.4	0.5593	1.84149	0.4930	0.238	1.450
	6H	9	9	0.6381	0.59883	93.8	0.4821	2.10452	0.3660	0.215	2.120
	7H	9	9	0.6203	0.40515	65.3	0.5063	1.98142	0.4170	0.239	1.290
	8H	9	9	0.6990	0.50385	72.1	0.5434	2.14173	0.3970	0.244	1.440
	10H	9	9	0.6318	0.52626	83.3	0.4670	2.30320	0.4510	0.149	1.780
	12H	9	9	0.7850	0.51311	65.4	0.6231	2.13741	0.8430	0.220	1.690
	14H	9	9	0.8909	0.60851	68.3	0.7309	1.94514	0.7750	0.297	2.080
	16H	9	9	1.0051	0.49241	49.0	0.8930	1.69568	1.0200	0.441	1.690
	18H	9	9	0.9699	0.45472	46.9	0.8590	1.73615	1.1100	0.357	1.540
	20H	9	9	0.9627	0.52371	54.4	0.8240	1.87126	1.0600	0.273	1.940
	22H	9	9	0.7457	0.41963	56.3	0.6414	1.81633	0.6860	0.271	1.450
	23.5H	9	9	0.6751	0.30935	45.8	0.6187	1.54714	0.5870	0.374	1.260
Day 28	4H	9	9	0.6501	0.33546	51.6	0.5898	1.57382	0.6110	0.306	1.450
	8H	9	9	0.9154	0.50750	55.4	0.7880	1.83625	0.8720	0.285	1.940
	12H	9	9	0.9857	0.53062	53.8	0.8741	1.67978	0.9300	0.398	2.140
Day 29	0H	12	12	0.8323	0.49058	58.9	0.6904	1.98820	0.7905	0.185	1.930
	4H	12	12	0.5280	0.23157	43.9	0.4816	1.57708	0.4215	0.206	0.892

	8H	12	12	0.6492	0.37254	57.4	0.5579	1.79230	0.5430	0.200	1.340
	12H	12	12	0.7147	0.33321	46.6	0.6404	1.65449	0.6585	0.295	1.240
Day 30	0H	11	11	0.8924	0.30631	34.3	0.8464	1.40745	0.8610	0.495	1.520
	1H	11	11	0.7264	0.35752	49.2	0.6565	1.59424	0.6090	0.348	1.530
	2H	11	11	0.6491	0.21364	32.9	0.6178	1.39147	0.6190	0.390	0.974
	4H	11	11	0.6865	0.33996	49.5	0.6107	1.67154	0.6760	0.307	1.210
	5H	11	11	0.7082	0.40994	57.9	0.6160	1.72547	0.5880	0.297	1.600
	6H	11	11	0.6519	0.33980	52.1	0.5638	1.80838	0.6090	0.212	1.250
	7H	11	11	0.7899	0.51478	65.2	0.6252	2.13852	0.7930	0.207	1.730
	8H	11	11	0.9367	0.58856	62.8	0.7401	2.17202	0.8650	0.233	1.780
	10H	11	11	0.7395	0.50770	68.7	0.5829	2.11814	0.6200	0.189	1.770
	12H	11	11	0.8881	0.77808	87.6	0.6636	2.20837	0.6830	0.218	2.900
	14H	11	11	1.0653	0.92586	86.9	0.8037	2.17880	0.8560	0.258	3.450
	16H	11	11	0.9864	0.51673	52.4	0.8481	1.85590	0.9840	0.245	2.040
	18H	11	11	1.1151	0.65786	59.0	0.9251	2.00820	1.0400	0.207	2.620
	20H	11	11	1.1024	0.60757	55.1	0.9228	1.99273	1.1800	0.211	2.380
	22H	11	11	0.9143	0.60935	66.6	0.7273	2.11695	0.7180	0.177	2.040
	23.5H	11	11	0.7845	0.43513	55.5	0.6564	1.98755	0.6800	0.152	1.590
Days 27 & 30 Combined	0H	20	20	0.8355	0.27418	32.8	0.7927	1.40162	0.8425	0.429	1.520
	1H	20	20	0.7128	0.29865	41.9	0.6572	1.51580	0.6775	0.337	1.530
	2H	20	20	0.6587	0.21398	32.5	0.6249	1.40321	0.6350	0.326	1.040
	4H	20	20	0.7109	0.43544	61.3	0.6061	1.77284	0.6215	0.234	1.970
	5H	20	20	0.6862	0.39761	57.9	0.5898	1.75445	0.5405	0.238	1.600
	6H	20	20	0.6457	0.46023	71.3	0.5254	1.91808	0.5745	0.212	2.120
	7H	20	20	0.7136	0.46484	65.1	0.5686	2.04611	0.6965	0.207	1.730
	8H	20	20	0.8298	0.55130	66.4	0.6440	2.14976	0.7915	0.233	1.780
	10H	20	20	0.6910	0.50527	73.1	0.5275	2.17303	0.5420	0.149	1.780
	12H	20	20	0.8417	0.65746	78.1	0.6451	2.13366	0.6960	0.218	2.900
	14H	20	20	0.9868	0.78422	79.5	0.7701	2.03948	0.8180	0.258	3.450
	16H	20	20	0.9948	0.49266	49.5	0.8681	1.75967	0.9970	0.245	2.040
	18H	20	20	1.0498	0.56598	53.9	0.8947	1.86048	1.0750	0.207	2.620
	20H	20	20	1.0395	0.56111	54.0	0.8769	1.91021	1.1200	0.211	2.380
	22H	20	20	0.8384	0.52628	62.8	0.6873	1.95602	0.7020	0.177	2.040
	23.5H	20	20	0.7353	0.37824	51.4	0.6392	1.77529	0.6685	0.152	1.590

Application Site = Abdomen

Day	Time	n	# Obs. >LOQ	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 25	0H	12	12	0.8559	0.38007	44.4	0.7614	1.72897	0.7580	0.224	1.340
	4H	12	12	0.5725	0.33593	58.7	0.4801	1.94032	0.5070	0.109	1.340
	8H	12	12	0.6619	0.49938	75.4	0.5231	2.02481	0.4540	0.180	1.810
	12H	11	11	0.7678	0.59324	77.3	0.5923	2.15139	0.6440	0.208	2.210

Day 26	0H	11	11	1.0170	0.65848	64.7	0.8238	2.04230	1.0900	0.223	2.470
	4H	11	11	0.9453	0.61240	64.8	0.7860	1.90388	0.7580	0.267	2.300
	8H	11	11	0.9732	0.64445	66.2	0.7493	2.27998	0.9140	0.151	1.980
	12H	11	11	1.0673	0.66268	62.1	0.8841	1.97633	0.8750	0.209	2.580
Day 27	0H	11	11	0.9265	0.51511	55.6	0.8158	1.67838	0.7240	0.432	1.960
	1H	11	11	0.6864	0.28320	41.3	0.6332	1.53213	0.6280	0.333	1.200
	2H	11	11	0.6846	0.34457	50.3	0.6064	1.69019	0.5580	0.275	1.270
	4H	11	11	0.9067	0.66590	73.4	0.7424	1.89613	0.7080	0.338	2.570
	5H	11	11	0.8715	0.69574	79.8	0.7018	1.94180	0.7360	0.286	2.750
	6H	11	11	0.8515	0.60073	70.5	0.7041	1.87712	0.6780	0.283	2.340
	7H	11	11	0.9251	0.85810	92.8	0.7189	1.98763	0.6800	0.304	3.350
	8H	11	11	0.8564	0.52352	61.1	0.7264	1.88449	0.8360	0.173	2.210
	10H	11	11	0.9087	0.47489	52.3	0.8157	1.60445	0.7660	0.468	1.900
	12H	11	11	0.9115	0.39041	42.8	0.8482	1.47127	0.7630	0.498	1.820
	14H	11	11	0.9315	0.49896	53.6	0.8403	1.58290	0.8160	0.388	2.260
	16H	11	11	1.0727	0.42625	39.7	1.0035	1.45818	0.9040	0.613	1.960
	18H	11	11	1.0615	0.35591	33.5	1.0055	1.42014	1.0800	0.606	1.620
	20H	11	11	1.0844	0.41945	38.7	1.0182	1.44293	0.9620	0.584	1.980
	22H	11	11	1.0067	0.48036	47.7	0.9105	1.59773	0.8040	0.463	1.880
	23.5H	11	11	0.9287	0.59391	63.9	0.8065	1.69713	0.7200	0.421	2.500
Day 28	4H	10	10	0.6127	0.25358	41.4	0.5715	1.47709	0.5975	0.284	1.220
	8H	10	10	0.6547	0.35608	54.4	0.5802	1.65843	0.4790	0.332	1.350
	12H	10	10	0.8782	0.45510	51.8	0.7665	1.76318	0.9055	0.366	1.670
Day 29	0H	10	10	1.0294	0.43246	42.0	0.9445	1.56797	0.9940	0.423	1.780
	4H	10	10	0.6672	0.38443	57.6	0.5958	1.60208	0.5485	0.356	1.620
	8H	10	10	0.8180	0.42471	51.9	0.7379	1.59032	0.6350	0.373	1.780
	12H	10	10	0.9772	0.62645	64.1	0.8403	1.73878	0.7780	0.458	2.380
Day 30	0H	9	9	0.6223	0.35642	57.3	0.5340	1.83375	0.4960	0.170	1.220
	1H	9	9	0.5937	0.41692	70.2	0.4753	2.04532	0.4740	0.165	1.300
	2H	9	9	0.5682	0.35033	61.7	0.4613	2.05524	0.4990	0.182	1.090
	4H	9	9	0.5613	0.36307	64.7	0.4531	2.06279	0.5990	0.158	1.190
	5H	9	9	0.5039	0.26008	51.6	0.4307	1.89151	0.5850	0.151	0.794
	6H	9	9	0.4732	0.25628	54.2	0.4137	1.74385	0.3460	0.178	0.851
	7H	9	9	0.5576	0.23738	42.6	0.5042	1.66077	0.5430	0.199	0.899
	8H	9	9	0.6087	0.21507	35.3	0.5734	1.45199	0.5930	0.326	0.880
	10H	9	9	0.5918	0.18376	31.1	0.5631	1.41664	0.6020	0.285	0.847
	12H	9	9	0.5992	0.24044	40.1	0.5619	1.44860	0.5450	0.353	1.020
	14H	9	9	0.6353	0.22602	35.6	0.6032	1.40225	0.6200	0.347	1.120
	16H	9	9	0.7680	0.27706	36.1	0.7242	1.44498	0.6800	0.370	1.290
	18H	9	9	0.7886	0.30936	39.2	0.7428	1.42577	0.6800	0.495	1.320
	20H	9	9	0.6752	0.18458	27.3	0.6532	1.31491	0.6320	0.435	0.971
	22H	9	9	0.6586	0.27135	41.2	0.6128	1.49041	0.5530	0.365	1.190
	23.5H	9	9	0.6134	0.32518	53.0	0.5450	1.66356	0.4150	0.282	1.210

Days											
27 & 30 Combined	0H	20	20	0.7896	0.46609	59.0	0.6742	1.79574	0.6340	0.170	1.960
	1H	20	20	0.6446	0.34299	53.2	0.5565	1.78054	0.5870	0.165	1.300
	2H	20	20	0.6323	0.34307	54.3	0.5362	1.85679	0.5390	0.182	1.270
	4H	20	20	0.7513	0.56565	75.3	0.5945	2.02775	0.6065	0.158	2.570
	5H	20	20	0.7061	0.56431	79.9	0.5634	1.97759	0.6785	0.151	2.750
	6H	20	20	0.6813	0.50486	74.1	0.5543	1.90097	0.5005	0.178	2.340
	7H	20	20	0.7597	0.66818	88.0	0.6129	1.86655	0.6615	0.199	3.350
	8H	20	20	0.7449	0.42392	56.9	0.6531	1.70461	0.7465	0.173	2.210
	10H	20	20	0.7661	0.39885	52.1	0.6904	1.57175	0.7060	0.285	1.900
	12H	20	20	0.7710	0.36052	46.8	0.7048	1.52931	0.6750	0.353	1.820
	14H	20	20	0.7983	0.41881	52.5	0.7238	1.54236	0.6715	0.347	2.260
	16H	20	20	0.9356	0.39005	41.7	0.8665	1.49115	0.8085	0.370	1.960
	18H	20	20	0.9387	0.35548	37.9	0.8774	1.45693	0.7955	0.495	1.620
	20H	20	20	0.9003	0.38801	43.1	0.8338	1.47996	0.7910	0.435	1.980
	22H	20	20	0.8501	0.42899	50.5	0.7619	1.60433	0.7700	0.365	1.880
	23.5H	20	20	0.7869	0.50603	64.3	0.6761	1.72350	0.6775	0.282	2.500

Application Site = Flank

Day	Time	n	# Obs. >LOQ	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 25	0H	9	9	0.6722	0.29287	43.6	0.6120	1.61551	0.6290	0.238	1.170
	4H	9	9	0.7684	0.52305	68.1	0.6275	2.02705	0.7370	0.159	1.980
	8H	9	9	1.0453	0.73978	70.8	0.8723	1.85081	0.7130	0.376	2.780
	12H	9	9	1.1301	0.57397	50.8	1.0344	1.52769	0.9720	0.565	2.530
Day 26	0H	10	10	0.5991	0.51432	85.8	0.4750	1.92537	0.4065	0.239	1.810
	4H	10	10	0.7246	0.66163	91.3	0.5297	2.21190	0.3775	0.232	2.050
	8H	10	10	0.8006	0.65923	82.3	0.5965	2.24353	0.5675	0.219	2.120
	12H	10	10	0.8713	0.55705	63.9	0.6991	2.11591	0.7015	0.167	1.860
Day 27	0H	12	12	1.0206	0.59848	58.6	0.8713	1.81989	0.9135	0.339	2.190
	1H	12	12	0.8854	0.48531	54.8	0.7686	1.76217	0.8550	0.321	1.900
	2H	12	12	0.7239	0.32666	45.1	0.6551	1.61715	0.6995	0.272	1.320
	4H	12	12	0.7117	0.41155	57.8	0.6366	1.59337	0.6350	0.335	1.890
	5H	12	12	0.7970	0.61097	76.7	0.6506	1.88533	0.5595	0.276	2.460
	6H	12	12	0.8569	0.81012	94.5	0.5915	2.51432	0.7135	0.145	3.070
	7H	12	12	0.9963	0.92756	93.1	0.6780	2.54736	0.6695	0.170	3.350
	8H	12	12	1.0207	0.95022	93.1	0.7304	2.34634	0.7845	0.177	3.600
	10H	12	12	1.1392	0.92575	81.3	0.8959	2.02851	1.0305	0.333	3.700
	12H	12	12	1.0202	0.94429	92.6	0.7286	2.34821	0.6125	0.173	3.530
	14H	12	12	1.3253	1.05047	79.3	0.9441	2.56498	0.9325	0.123	3.630
	16H	12	12	1.3274	0.89040	67.1	1.0127	2.32638	1.2750	0.185	2.830
	18H	12	12	1.1423	0.67794	59.4	0.8945	2.30262	1.1350	0.194	2.500

	20H	12	12	1.3704	0.96508	70.4	1.0214	2.41068	1.2950	0.198	3.380
	22H	12	12	1.2376	1.10689	89.4	0.9098	2.23945	0.9500	0.339	4.180
	23.5H	12	12	1.1897	1.30093	109.4	0.7457	2.70731	0.6040	0.170	4.610
Day 28	4H	12	12	0.9311	1.07976	116.0	0.6766	2.05352	0.5450	0.323	4.230
	8H	12	12	0.9149	0.90740	99.2	0.6574	2.30859	0.6595	0.143	3.540
	12H	12	12	0.8508	0.60145	70.7	0.7159	1.81436	0.8040	0.274	2.580
Day 29	0H	9	9	0.7540	0.35840	47.5	0.6774	1.64381	0.6460	0.386	1.290
	4H	9	9	0.5993	0.24232	40.4	0.5506	1.58457	0.6230	0.224	1.010
	8H	9	9	0.6587	0.31488	47.8	0.5870	1.69309	0.5640	0.245	1.090
	12H	9	9	0.8814	0.36184	41.1	0.8202	1.50138	0.8640	0.383	1.680
Day 30	0H	11	11	0.9399	0.40036	42.6	0.8191	1.89480	1.0100	0.166	1.380
	1H	11	11	0.7815	0.34249	43.8	0.6955	1.73588	0.8460	0.208	1.270
	2H	11	11	0.8638	0.37218	43.1	0.7512	1.89862	0.9500	0.162	1.410
	4H	11	11	0.7585	0.33664	44.4	0.6662	1.80852	0.8520	0.191	1.280
	5H	11	11	0.6801	0.29523	43.4	0.6189	1.59817	0.7060	0.300	1.140
	6H	11	11	0.7087	0.34400	48.5	0.6279	1.71641	0.6490	0.256	1.350
	7H	11	11	0.8363	0.62511	74.7	0.6834	1.91810	0.6000	0.210	2.470
	8H	11	11	0.8677	0.36331	41.9	0.7956	1.56690	0.8140	0.386	1.370
	10H	11	11	0.8692	0.36211	41.7	0.8047	1.50878	0.8050	0.435	1.600
	12H	11	11	0.8829	0.40916	46.3	0.8109	1.52540	0.7310	0.461	1.860
	14H	11	11	1.1887	0.52014	43.8	1.0588	1.73139	1.2000	0.332	2.030
	16H	11	11	1.0951	0.48695	44.5	0.9871	1.64244	0.9930	0.447	1.750
	18H	11	11	1.3349	0.70412	52.7	1.1748	1.71481	1.2700	0.491	2.660
	20H	11	11	1.1201	0.57443	51.3	0.9911	1.70965	1.0400	0.340	2.470
	22H	11	11	0.9278	0.48847	52.6	0.8199	1.69467	0.7730	0.334	2.020
	23.5H	11	11	1.0127	0.55687	55.0	0.8877	1.73559	1.0000	0.283	2.370
Days 27 & 30 Combined	0H	23	23	0.9820	0.50364	51.3	0.8460	1.83111	1.0000	0.166	2.190
	1H	23	23	0.8357	0.41702	49.9	0.7327	1.73144	0.8460	0.208	1.900
	2H	23	23	0.7908	0.34845	44.1	0.6994	1.74072	0.8080	0.162	1.410
	4H	23	23	0.7341	0.36982	50.4	0.6506	1.67916	0.7390	0.191	1.890
	5H	23	23	0.7411	0.47940	64.7	0.6352	1.73186	0.6050	0.276	2.460
	6H	23	23	0.7860	0.62263	79.2	0.6087	2.11154	0.6490	0.145	3.070
	7H	23	23	0.9197	0.78389	85.2	0.6806	2.21165	0.6000	0.170	3.350
	8H	23	23	0.9475	0.71942	75.9	0.7609	1.96642	0.8140	0.177	3.600
	10H	23	23	1.0100	0.71213	70.5	0.8511	1.77622	0.9110	0.333	3.700
	12H	23	23	0.9545	0.72584	76.0	0.7669	1.95351	0.7170	0.173	3.530
	14H	23	23	1.2600	0.82437	65.4	0.9973	2.14732	1.1700	0.123	3.630
	16H	23	23	1.2163	0.71991	59.2	1.0004	1.98274	1.1900	0.185	2.830
	18H	23	23	1.2344	0.68179	55.2	1.0190	2.02726	1.1900	0.194	2.660
	20H	23	23	1.2507	0.79500	63.6	1.0068	2.05398	1.2400	0.198	3.380
	22H	23	23	1.0894	0.86377	79.3	0.8656	1.96211	0.7730	0.334	4.180
	23.5H	23	23	1.1050	0.99766	90.3	0.8105	2.22842	0.7140	0.170	4.610

Summary statistics for $AUC_{0\text{-}t,ss}$ and $C_{max,\,ss}$ for unconjugated rotigotine for each patch application site using separated data for Day 27 and Day 30 are given in Table 17.

Table 17: Descriptive statistics of parameters of pharmacokinetics for rotigotine under multiple dose in patients with early-stage Parkinson's disease (H = hip, S = shoulder, UA = upper arm, T = thigh, AB = abdomen, F = flank)

Day Parameter	Site	n	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 27										
AUC 0-t, ss (ng*h/ml)	H	10	24.714	12.1148	49.0	22.284	1.6080	18.704	11.27	45.38
	S	11	21.147	9.9209	46.9	19.167	1.6046	17.603	7.51	43.51
	UA	10	23.846	12.6658	53.1	20.347	1.9076	20.963	5.13	46.50
	T	9	18.464	10.0154	54.2	15.994	1.7917	17.649	7.06	34.06
	AB	11	21.868	9.9971	45.7	20.228	1.4849	16.608	13.72	45.82
	F	12	25.438	17.4836	68.7	20.817	1.9421	20.727	6.73	68.64
AUC 0-t, ss, normalized (ng*h*kg/ml/mg)	H	10	263.38	132.896	50.5	239.15	1.567	231.03	125.6	581.9
	S	11	238.37	75.596	31.7	225.55	1.444	262.41	106.6	354.1
	UA	10	322.54	99.970	31.0	308.16	1.384	298.42	165.4	497.0
	T	9	222.62	84.993	38.2	207.97	1.488	227.07	118.7	372.0
	AB	11	316.61	233.860	73.9	262.54	1.859	232.01	89.3	952.1
	F	12	258.09	132.295	51.3	233.42	1.575	218.30	104.3	578.1
Maximum Concentration (ng/ml)	H	10	1.8159	1.19253	65.7	1.5354	1.80840	1.2250	0.679	4.440
	S	11	1.3583	0.57413	42.3	1.2418	1.59520	1.1900	0.431	2.580
	UA	10	1.4986	0.71726	47.9	1.3274	1.74189	1.4000	0.403	2.870
	T	9	1.1772	0.61214	52.0	1.0354	1.73314	1.1800	0.469	2.120
	AB	11	1.5598	0.81231	52.1	1.3953	1.62515	1.2100	0.775	3.350
	F	12	1.9218	1.10854	57.7	1.6674	1.74328	1.6500	0.683	4.610

Day Parameter	Site	n	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 27										
Maximum Conc normalized (ng*kg/ml/mg)	H	10	19.784	15.6559	79.1	16.478	1.7821	13.943	9.46	61.31
	S	11	15.493	5.0158	32.4	14.613	1.4647	15.873	6.12	22.37
	UA	10	21.552	8.7051	40.4	20.103	1.4770	19.225	11.16	39.01
	T	9	14.217	4.9198	34.6	13.464	1.4247	14.659	7.69	23.15
	AB	11	21.413	12.9134	60.3	18.110	1.8837	20.181	4.96	52.52
	F	12	20.022	8.2775	41.3	18.697	1.4562	16.847	10.58	38.83
Average Concentration (ng/ml)	H	10	1.0516	0.51553	49.0	0.9483	1.60805	0.7959	0.479	1.931
	S	11	0.8999	0.42217	46.9	0.8156	1.60465	0.7491	0.319	1.852
	UA	10	1.0147	0.53897	53.1	0.8658	1.90761	0.8920	0.218	1.979
	T	9	0.7857	0.42619	54.2	0.6806	1.79171	0.7510	0.300	1.449
	AB	11	0.9306	0.42541	45.7	0.8608	1.48493	0.7067	0.584	1.950
	F	12	1.0825	0.74398	68.7	0.8858	1.94211	0.8820	0.286	2.921
Time to Maximum Concentration (hours)	H	10	13.50	7.382	54.7	13.42	1.758	16.00	0.0	22.0
	S	11	13.45	7.699	57.2	15.65	1.456	18.00	0.0	20.0
	UA	10	9.60	9.324	97.1	14.97	1.520	9.00	0.0	22.0
	T	9	12.00	7.874	65.6	14.57	1.503	16.00	0.0	20.0
	AB	11	12.95	8.020	61.9	11.82	2.124	16.00	0.0	23.5
	F	12	13.71	8.516	62.1	11.65	2.478	16.00	0.0	23.5

Day Parameter	Site	n	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 27										
Peak-Trough Fluctuation (%)	H	10	114.3	43.18	37.8	107.3	1.45	104.2	61	198
	S	11	99.6	21.06	21.2	97.6	1.24	102.9	72	136
	UA	10	94.5	34.06	36.1	89.3	1.43	87.1	51	168
	T	9	95.0	24.11	25.4	92.0	1.32	105.9	57	124
	AB	11	116.6	70.07	60.1	104.7	1.56	88.3	60	314
	F	12	148.1	36.34	24.5	144.1	1.28	137.9	100	200
Half Value Duration (hour)	H	10	16.39	6.414	39.1	14.87	1.670	17.67	4.9	23.5
	S	11	18.35	4.227	23.0	17.86	1.287	19.61	11.7	23.0
	UA	10	19.34	3.802	19.7	18.98	1.230	19.83	13.1	23.5
	T	9	18.42	3.690	20.0	18.10	1.217	16.05	14.7	23.5
	AB	11	17.93	6.295	35.1	15.05	2.339	20.45	1.2	23.5
	F	12	11.42	4.479	39.2	10.57	1.530	10.84	4.5	18.3
Apparent Dose of Rotigotine (mg)	H	10	6.861	2.0513	29.9	6.590	1.3500	6.305	4.12	10.33
	S	11	6.474	2.0421	31.5	6.155	1.4096	6.500	3.53	9.68
	UA	10	5.619	2.7460	48.9	4.824	1.9268	5.535	1.06	10.10
	T	9	6.438	2.9351	45.6	5.912	1.5345	5.130	3.48	11.57
	AB	11	6.369	2.4858	39 0	5.773	1.6789	7.090	1.61	9.38
	F	12	7.258	2.6769	36.9	6.883	1.3880	6.170	4.83	13.52

Day Parameter	Site	n	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 30										
AUC 0-t, ss (ng*h/ml)	H	10	22.916	13.4155	58.5	19.957	1.7352	19.954	8.49	54.54
	S	11	26.442	13.8860	52.5	23.741	1.6054	22.634	12.33	57.77
	UA	11	22.333	8.9481	40.1	20.795	1.4861	21.025	11.85	39.68
	T	11	20.713	11.8144	57.0	17.832	1.7938	18.354	7.37	46.16
	AB	9	14.776	5.2155	35.3	13.964	1.4308	14.797	8.85	23.22
	F	11	22.577	8.9371	39.6	20.789	1.5642	25.736	9.14	39.98
AUC 0-t, ss, normalized (ng*h*kg/ml/mg)	H	10	272.01	119.459	43.9	251.27	1.510	229.22	143.0	489.0
	S	11	239.26	102.668	42.9	219.73	1.553	206.37	93.3	421.7
	UA	11	218.21	50.674	23.2	212.44	1.284	218.78	121.8	299.8
	T	11	275.09	158.016	57.4	248.30	1.551	235.76	129.6	717.8
	AB	9	224.48	49.363	22.0	219.75	1.245	232.90	152.7	319.7
	F	11	255.07	110.435	43.3	233.60	1.561	218.91	118.3	439.1
Maximum Concentration (ng/ml)	H	10	1.7803	1.40713	79.0	1.4347	1.94153	1.3150	0.598	5.310
	S	11	1.8044	1.20853	67.0	1.5544	1.70345	1.3900	0.874	4.810
	UA	11	1.4595	0.63351	43.4	1.3509	1.49873	1.2900	0.747	2.830
	T	11	1.4849	0.78230	52.7	1.3303	1.62641	1.2500	0.555	3.450
	AB	9	0.9682	0.31038	32.1	0.9190	1.42608	1.0100	0.502	1.320
	F	11	1.5509	0.71145	45.9	1.3920	1.66366	1.4300	0.583	2.660

Day Parameter	Site	n	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 30										
Maximum Conc normalized (ng*kg/ml/mg)	H	10	20.128	11.2346	55.8	18.063	1.5895	15.754	10.08	47.61
	S	11	16.303	8.9019	54.6	14.386	1.6858	14.201	5.60	35.11
	UA	11	14.249	3.5763	25.1	13.801	1.3154	14.711	7.68	19.46
	T	11	20.719	12.0527	58.2	18.523	1.5976	16.694	8.59	53.65
	AB	9	14.874	4.0113	27.0	14.462	1.2751	13.548	11.17	23.78
	F	11	17.834	9.3068	52.2	15.642	1.7272	16.666	7.25	35.23
Average Concentration (ng/ml)	H	10	0.9752	0.57087	58.5	0.8493	1.73518	0.8491	0.361	2.321
	S	11	1.1252	0.59089	52.5	1.0102	1.60542	0.9631	0.525	2.458
	UA	11	0.9503	0.38077	40.1	0.8849	1.48608	0.8947	0.504	1.688
	T	11	0.8814	0.50274	57.0	0.7588	1.79383	0.7810	0.314	1.964
	AB	9	0.6287	0.22194	35.3	0.5942	1.43075	0.6296	0.377	0.988
	F	11	0.9607	0.38030	39.6	0.8846	1.56423	1.0951	0.389	1.701
Time to Maximum Concentration (hours)	H	10	14.75	9.145	62.0	17.28	1.553	18.00	0.0	23.5
	S	11	12.36	6.281	50.8	10.86	1.731	12.00	5.0	22.0
	UA	11	15.55	5.087	32.7	14.54	1.525	16.00	5.0	22.0
	T	11	13.82	7.872	57.0	16.26	1.366	16.00	0.0	22.0
	AB	9	13.44	7.468	55.6	9.54	3.054	16.00	1.0	22.0
	F	11	16.41	5.324	32.4	15.43	1.485	18.00	7.0	23.5

Day Parameter	Site	n	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Day 30										
Peak-Trough Fluctuation (%)	H	10	120.5	45.13	37.4	113.3	1.45	102.4	65	185
	S	11	110.8	30.52	27.5	107.3	1.30	101.6	78	171
	UA	11	101.4	24.49	24.2	98.7	1.28	104.6	66	144
	T	11	127.6	78.15	61.2	111.7	1.67	90.7	60	312
	AB	9	100.7	34.78	34.6	95.5	1.41	86.2	59	154
	F	11	103.9	44.17	42.5	95.5	1.55	89.8	43	195
Half Value Duration (hour)	H	10	15.06	6.103	40.5	13.50	1.740	15.43	3.8	23.5
	S	11	18.34	4.563	24.9	17.72	1.339	20.36	9.6	22.8
	UA	11	18.14	3.700	20.4	17.76	1.252	18.46	10.8	23.2
	T	11	16.03	7.689	48.0	12.71	2.410	19.52	2.0	23.5
	AB	9	18.49	4.616	25.0	17.92	1.317	20.20	10.7	23.5
	F	11	16.71	6.323	37.8	15.37	1.584	18.78	5.7	23.5
Apparent Dose of Rotigotine (mg)	H	10	6.230	2.1042	33.8	5.886	1.4409	6.555	3.36	9.30
	S	11	8.157	1.9871	24.4	7.948	1.2679	7.480	5.91	11.20
	UA	11	7.034	1.5860	22.5	6.875	1.2508	6.920	4.92	10.21
	T	11	5.521	1.7372	31.5	5.232	1.4356	5.460	2.55	7.78
	AB	9	4.802	1.4404	30.0	4.623	1.3356	4.350	3.22	7.22
	F	11	7.555	2.0697	27.4	7.291	1.3270	8.300	4.63	11.19

Day Parameter	Site	n	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Days 27 and 30 combined										
AUC 0-t, ss (ng*h/ml)	H	20	23.815	12.4750	52.4	21.089	1.6552	19.491	8.49	54.54
	S	22	23.794	12.0843	50.8	21.332	1.6073	21.304	7.51	57.77
	UA	21	23.053	10.6219	46.1	20.580	1.6754	21.025	5.13	46.50
	T	20	19.701	10.8174	54.9	16.980	1.7700	18.002	7.06	46.16
	AB	20	18.677	8.7841	47.0	17.121	1.5141	16.233	8.85	45.82
	F	23	24.069	13.8303	57.5	20.803	1.7470	23.025	6.73	68.64
AUC 0-t, ss, normalized (ng*h*kg/ml/mg)	H	20	267.69	123.066	46.0	245.13	1.522	229.22	125.6	581.9
	S	22	238.82	87.983	36.8	222.62	1.486	249.31	93.3	421.7
	UA	21	267.89	92.907	34.7	253.61	1.403	244.24	121.8	497.0
	T	20	251.48	130.002	51.7	229.27	1.521	232.36	118.7	717.8
	AB	20	275.15	178.946	65.0	242.34	1.617	232.46	89.3	952.1
	F	23	256.64	119.570	46.6	233.51	1.553	218.91	104.3	578.1
Maximum Concentration (ng/ml)	H	20	1.7981	1.26959	70.6	1.4842	1.84629	1.3150	0.598	5.310
	S	22	1.5813	0.95110	60.1	1.3893	1.65227	1.3250	0.431	4.810
	UA	21	1.4781	0.65771	44.5	1.3396	1.59938	1.2900	0.403	2.870
	T	20	1.3465	0.71031	52.8	1.1884	1.67848	1.2100	0.469	3.450
	AB	20	1.2936	0.69212	53.5	1.1563	1.60286	1.0950	0.502	3.350
	F	23	1.7444	0.93829	53.8	1.5295	1.69863	1.4300	0.583	4.610

Day Parameter	Site	n	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Days 27 and 30 combined										
Maximum Conc normalized (ng*kg/ml/mg)	H	20	19.956	13.2635	66.5	17.253	1.6685	15.577	9.46	61.31
	S	22	15.898	7.0630	44.4	14.499	1.5627	15.328	5.60	35.11
	UA	21	17.727	7.3798	41.6	16.508	1.4597	15.499	7.68	39.01
	T	20	17.793	9.8823	55.5	16.046	1.5548	15.506	7.69	53.65
	AB	20	18.470	10.2802	55.7	16.367	1.6473	14.906	4.96	52.52
	F	23	18.976	8.6532	45.6	17.168	1.5894	16.666	7.25	38.83
Average Concentration (ng/ml)	H	20	1.0134	0.53085	52.4	0.8974	1.65522	0.8294	0.361	2.321
	S	22	1.0125	0.51423	50.8	0.9077	1.60729	0.9065	0.319	2.458
	UA	21	0.9810	0.45199	46.1	0.8758	1.67538	0.8947	0.218	1.979
	T	20	0.8383	0.46031	54.9	0.7226	1.76997	0.7660	0.300	1.964
	AB	20	0.7947	0.37379	47.0	0.7286	1.51410	0.6908	0.377	1.950
	F	23	1.0242	0.58853	57.5	0.8853	1.74705	0.9798	0.286	2.921
Time to Maximum Concentration (hours)	H	20	14.13	8.114	57.4	15.12	1.666	17.00	0.0	23.5
	S	22	12.91	6.879	53.3	12.80	1.653	15.00	0.0	22.0
	UA	21	12.71	7.830	61.6	14.69	1.504	14.00	0.0	22.0
	T	20	13.00	7.719	59.4	15.50	1.417	16.00	0.0	22.0
	AB	20	13.18	7.576	57.5	10.68	2.514	16.00	0.0	23.5
	F	23	15.00	7.145	47.6	13.40	2.010	16.00	0.0	23.5

Day Parameter	Site	n	Mean	SD	CV (%)	Geo. Mean	Geo. SD	Median	Min	Max
Days 27 and 30 combined										
Peak-Trough Fluctuation (%)	H	20	117.4	43.10	36.7	110.3	1.44	102.5	61	198
	S	22	105.2	26.22	24.9	102.3	1.27	102.2	72	171
	UA	21	98.1	28.89	29.5	94.1	1.35	93.8	51	168
	T	20	112.9	61.12	54.1	102.4	1.53	98.5	57	312
	AB	20	109.4	56.21	51.4	100.4	1.48	88.0	59	314
	F	23	127.0	45.34	35.7	118.4	1.49	123.5	43	200
Half Value Duration (hour)	H	20	15.73	6.132	39.0	14.17	1.685	15.95	3.8	23.5
	S	22	18.35	4.292	23.4	17.79	1.305	20.33	9.6	23.0
	UA	21	18.71	3.705	19.8	18.33	1.239	18.64	10.8	23.5
	T	20	17.11	6.192	36.2	14.90	1.965	19.23	2.0	23.5
	AB	20	18.18	5.469	30.1	16.28	1.912	20.33	1.2	23.5
	F	23	13.95	5.959	42.7	12.64	1.604	12.47	4.5	23.5
Apparent Dose of Rotigotine (mg)	H	20	6.546	2.0483	31.3	6.228	1.3916	6.455	3.36	10.33
	S	22	7.315	2.1468	29.3	6.994	1.3721	7.270	3.53	11.20
	UA	21	6.360	2.2749	35.8	5.808	1.6512	6.360	1.06	10.21
	T	20	5.934	2.3312	39.3	5.528	1.4728	5.245	2.55	11.57
	AB	20	5.664	2.1830	38.5	5.223	1.5453	5.000	1.61	9.38
	F	23	7.400	2.3565	31.8	7.075	1.3521	7.090	4.63	13.52

Table 18 shows the summary statistics for $AUC_{0\text{-}t,ss}$ and $C_{max,\ ss}$ for unconjugated rotigotine for each site combined data from Day 27 and Day 30.

Table 18: Summary statistics of derived PK parameters for area under the curve ($AUC_{0\text{-}t,ss,normalized}$) and maximum plasma concentration ($C_{max,normalized}$) of unconjugated rotigotine for each patch application site after normalization for body weight and apparent dose, data from Day 27 and Day 30 combined (PKS)

Application Site	n	Mean (SD)	CV (%)	Geometric mean (SD)	Median	Range
$AUC_{0\text{-}t,ss,normalized}$ (ng*h*kg/mL/mg)						
Hip	20	267.69 (123.066)	46.0	245.13 (1.522)	229.22	125.6-581.9
Shoulder	22	238.82 (87.983)	36.8	222.62 (1.486)	249.31	93.3-421.7
Upper arm	21	267.89 (92.907)	34.7	253.61 (1.403)	244.24	121.8-497.0
Thigh	20	251.48 (130.002)	51.7	229.27 (1.521)	232.36	118.7-717.8
Abdomen	20	275.15 (178.946)	65.0	242.34 (1.617)	232.46	89.3-952.1
Flank	23	256.64 (119.570)	46.6	233.51 (1.553)	218.91	104.3-578.1
$C_{max,ss,\ normalized}$ (ng*kg/mL/mg)						
Hip	20	19.956 (13.2635)	66.5	17.253 (1.6685)	15.577	9.46-61.31
Shoulder	22	15.898 (7.0630)	44.4	14.499 (1.5627)	15.328	5.60-35.11
Upper arm	21	17.727 (7.3798)	41.6	16.508 (1.4597)	15.499	7.68-39.01
Thigh	20	17.793 (9.8823)	55.5	16.046 (1.5548)	15.506	7.69-53.65
Abdomen	20	18.470 (10.2802)	55.7	16.367 (1.6473)	14.906	4.96-52.52
Flank	23	18.976 (8.6532)	45.6	17.168 (1.5894)	16.666	7.25-38.83

PKS = pharmacokinetic set; SD = standard deviation; CV = coefficient of variance

EXAMPLE 5

[0093] A multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel group clinical trial was performed to evaluate the safety and efficacy of a rotigotine patch in subjects with early stage, idiopathic Parkinson's disease. . The silicone transdermal patches were made in accordance with the teachings of U.S. Patent Application Publication No. US 2003/0026830 at paragraphs 38-42, U.S. Patent Application Publication No. US 2003/0027793 at paragraphs 37-41 and U.S. Patent No. 6,884,434, columns 5-6, Example 2 and comprised the following layers and components:

Patches D, E and F

Name of Ingredient	Patch D (mg/10 cm^2 patch)	Patch E (mg/20 cm^2 patch)	Patch F (mg/30 cm^2 patch)
Rotigotine	4.50	9.00	13.50
Silicone adhesive 4301	22.24	44.47	66.71
Silicone adhesive 4201	22.23	44.46	66.70
Providone	1.00	2.00	3.00
Sodium metabisulfite	0.00045	0.0009	0.00135
Ascorbyl palmitate	0.010	0.02	0.03
Vitamin E (DL-α-tocopherol)	0.025	0.05	0.075
Backing foil PET, siliconized aluminized, color coated	10 cm^2	20 cm^2	30 cm^2
Ink Bargofor 70135-1-P	As much as needed	As much as needed	As much as needed

[0094] The doses included 4.5mg/day, 9mg/day, and 13.5mg/day of rotigotine. Trial periods consisted of a 4-week pre-treatment (washout) period, a 3-week dose escalation period, a 25-week dose maintenance period, and a 4-week follow-up period for a total duration of 36 weeks.

[0095] Plasma samples for measurement of rotigotine concentration were collected in 56 subjects. The total number of samples was 1297. During the study blood samples for the analysis of rotigotine were taken before patch application and at 1, 2, 3, 11, 19, and 28 weeks after first patch application.

[0096] Table 19 shows the results of descriptive statistics for concentrations of rotigotine in plasma samples. Figure 10 illustrates the results. This figure shows stable concentration over the maintenance phase of the study.

Table 19: Descriptive statistics of rotigotine plasma concentrations (ng/mL) during titration and maintenance phase

Day Period	Dose (mg/day)	Sampling Time	n	Mean	SD	Median	Min	Max
Day8 TP	4.5	Prior removal	54	0.270	0.234	0.222	0.024	1.670
Day 15 TP	9.0	Prior removal	51	0.508	0.272	0.435	0.053	1.580
Day 1 MP	13.5	Prior removal	48	0.757	0.430	0.714	0.064	2.130
Day 57 MP	13.5	Prior removal	45	0.824	0.459	0.702	0.103	2.070
Day 113 MP	13.5	Prior removal	41	0.825	0.483	0.713	0.122	2.420
End of MP	13.5	Prior removal	39	0.788	0.382	0.729	0.282	1.800

Min=minimum; Max=maximum; MP=maintenance period; SD=standard deviation
TP=titration period.

WHAT IS CLAIMED IS

1. A method for treating Parkinson's Disease in a human patient, comprising administering to the patient a rotigotine formulation capable of providing a plasma concentration effective to alleviate the symptoms of Parkinson's Disease, wherein the C_{max} is from about 0.14 ng/mL to about 1.54 ng/mL and wherein the mean area under the curve (AUC_{0-t}) is from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

2. The method of claim 1, wherein the rotigotine is transdermally administered.

3. The method of claim 1, wherein the C_{max} is from about about 0.20 ng/mL to about 1.30 ng/mL.

4. The method of claim 1, wherein the C_{max} is from about 0.30 ng/mL to about 1.20 ng/mL.

5. The method of claim 1, wherein the C_{max} is from about 0.14 ng/mL to about 0.48 ng/mL.

6. The method of claim 1, wherein the C_{max} is from about 0.37 ng/mL to about 0.75 ng/mL.

7. The method of claim 1, wherein the C_{max} is from about 0.84 ng/mL to about 1.54 ng/mL.

8. The method of claim 1, wherein the C_{max} is about 0.31 ng/mL.

9. The method of claim 1, wherein the C_{max} is about 0.56 ng/mL.

10. The method of claim 1, wherein the C_{max} is about 1.19 ng/mL.

11. The method of claim 1, wherein the AUC_{0-t} is from about 4.0 ng/mL *h to about 30.0 ng/mL *h.

12. The method of claim 1, wherein the AUC_{0-t} is from about 5.0 ng/mL *h to about 25.0 ng/mL *h.

13. The method of claim 1, wherein the AUC_{0-t} is from about 3.3 ng/mL *h to about 8.9 ng/mL *h.

14. The method of claim 1, wherein the AUC_{0-t} is from about 7 ng/mL *h to about 15.2 ng/mL *h.

15. The method of claim 1, wherein the AUC_{0-t} is from about 15.2 ng/mL *h to about 32.2 ng/mL *h.

16. The method of claim 1, wherein the AUC_{0-t} is about 6.1 ng/mL *h.

17. The method of claim 1, wherein the AUC_{0-t} is about 11.1 ng/mL *h.

18. The method of claim 1, wherein the AUC_{0-t} is about 23.7 ng/mL *h.

19. The method of claim 1, wherein the method provides the plasma concentration effective to alleviate the symptoms of Parkinson's disease regardless of where the rotigotine is administered to the body of the human patient.

20. A method for treating Parkinson's Disease in a human patient, comprising administering to the patient a rotigotine formulation capable of maintaining a plasma concentration effective to alleviate the symptoms of Parkinson's Disease, wherein the C_{max} is sustained at a level from about 0.14 ng/mL to about 1.54 ng/mL and wherein the mean area under the curve (AUC_{o-t}) is from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

21. The method of claim 20, wherein the rotigotine is transdermally administered.

22. The method of claim 20, wherein the C_{max} is from about about 0.20 ng/mL to about 1.30 ng/mL.

23. The method of claim 20, wherein the C_{max} is from about 0.30 ng/mL to about 1.20 ng/mL.

24. The method of claim 20, wherein the C_{max} is from about 0.14 ng/mL to about 0.48 ng/mL.

25. The method of claim 20, wherein the C_{max} is from about 0.37 ng/mL to about 0.75 ng/mL.

26. The method of claim 20, wherein the C_{max} is from about 0.84 ng/mL to about 1.54 ng/mL.

27. The method of claim 20, wherein the C_{max} is about 0.31 ng/mL.

28. The method of claim 20, wherein the C_{max} is about 0.56 ng/mL.

29. The method of claim 20, wherein the C_{max} is about 1.19 ng/mL.

30. The method of claim 20, wherein the AUC_{0-t} is from about 4.0 ng/mL *h to about 30.0 ng/mL *h.

31. The method of claim 20, wherein the AUC_{0-t} is from about 5.0 ng/mL *h to about 25.0 ng/mL *h.

32. The method of claim 20, wherein the AUC_{0-t} is from about 3.3 ng/mL *h to about 8.9 ng/mL *h.

33. The method of claim 20, wherein the AUC_{0-t} is from about 7 ng/mL *h to about 15.2 ng/mL *h.

34. The method of claim 20, wherein the AUC_{0-t} is from about 15.2 ng/mL *h to about 32.2 ng/mL *h.

35. The method of claim 20, wherein the AUC_{0-t} is about 6.1 ng/mL *h.

36. The method of claim 20, wherein the AUC_{0-t} is about 11.1 ng/mL *h.

37. The method of claim 20, wherein the AUC_{0-t} is about 23.7 ng/mL *h.

38. The method of claim 20, wherein the method provides the plasma concentration effective to alleviate the symptoms of Parkinson's disease regardless of where the rotigotine is administered to the body of the human patient.

39. A method of treating Parkinson's Disease in a human patient, comprising applying a transdermal therapeutic system (TTS) comprising rotigotine, wherein the TTS is capable of providing a plasma concentration effective to alleviate the symptoms of Parkinson's Disease, wherein the C_{max} is from about 0.14 ng/mL to about 1.54 ng/mL and wherein the mean area under the curve (AUC_{0-t}) is from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

40. The method of claim 39, wherein the C_{max} is from about about 0.20 ng/mL to about 1.30 ng/mL.

41. The method of claim 39, wherein the C_{max} is from about 0.30 ng/mL to about 1.20 ng/mL.

42. The method of claim 39, wherein the C_{max} is from about 0.14 ng/mL to about 0.48 ng/mL.

43. The method of claim 39, wherein the C_{max} is from about 0.37 ng/mL to about 0.75 ng/mL.

44. The method of claim 39, wherein the C_{max} is from about 0.84 ng/mL to about 1.54 ng/mL.

45. The method of claim 39, wherein the C_{max} is about 0.31 ng/mL.

46. The method of claim 39, wherein the C_{max} is about 0.56 ng/mL.

47. The method of claim 39, wherein the C_{max} is about 1.19 ng/mL.

48. The method of claim 39, wherein the AUC_{0-t} is from about 4.0 ng/mL *h to about 30.0 ng/mL *h.

49. The method of claim 39, wherein the AUC_{0-t} is from about 5.0 ng/mL *h to about 25.0 ng/mL *h.

50. The method of claim 39, wherein the AUC_{0-t} is from about 3.3 ng/mL *h to about 8.9 ng/mL *h.

51. The method of claim 39, wherein the AUC_{0-t} is from about 7 ng/mL *h to about 15.2 ng/mL *h.

52. The method of claim 39, wherein the AUC_{0-t} is from about 15.2 ng/mL *h to about 32.2 ng/mL *h.

53. The method of claim 39, wherein the AUC_{0-t} is about 6.1 ng/mL *h.

54. The method of claim 39, wherein the AUC_{0-t} is about 11.1 ng/mL *h.

55. The method of claim 39, wherein the AUC_{0-t} is about 23.7 ng/mL *h.

56. The method of claim 39, wherein the method provides the plasma concentration effective to alleviate the symptoms of Parkinson's disease regardless of where the rotigotine is administered to the body of the human patient.

57. A method for treating Parkinson's Disease in a human patient, comprising administering to the patient over a 24 hr period a rotigotine formulation capable of providing a plasma concentration effective to alleviate the symptoms of Parkinson's Disease, wherein the C_{max} is from about 0.14 ng/mL to about 1.54 ng/mL and the AUC_{0-t} is from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

58. The method of claim 57, wherein the rotigotine is transdermally administered.

59. The method of claim 57, wherein the C_{max} is from about about 0.20 ng/mL to about 1.30 ng/mL.

60. The method of claim 57, wherein the C_{max} is from about 0.30 ng/mL to about 1.20 ng/mL.

61. The method of claim 57, wherein the C_{max} is from about 0.14 ng/mL to about 0.48 ng/mL.

62. The method of claim 57, wherein the C_{max} is from about 0.37 ng/mL to about 0.75 ng/mL.

63. The method of claim 57, wherein the C_{max} is from about 0.84 ng/mL to about 1.54 ng/mL.

64. The method of claim 57, wherein the C_{max} is about 0.31 ng/mL.

65. The method of claim 57, wherein the C_{max} is about 0.56 ng/mL.

66. The method of claim 57, wherein the C_{max} is about 1.19 ng/mL.

67. The method of claim 57, wherein the AUC_{0-t} is from about 4.0 ng/mL *h to about 30.0 ng/mL *h.

68. The method of claim 57, wherein the AUC_{0-t} is from about 5.0 ng/mL *h to about 25.0 ng/mL *h.

69. The method of claim 57, wherein the AUC_{0-t} is from about 3.3 ng/mL *h to about 8.9 ng/mL *h.

70. The method of claim 57, wherein the AUC_{0-t} is from about 7 ng/mL *h to about 15.2 ng/mL *h.

71. The method of claim 57, wherein the AUC_{0-t} is from about 15.2 ng/mL *h to about 32.2 ng/mL *h.

72. The method of claim 57, wherein the AUC_{0-t} is about 6.1 ng/mL *h.

73. The method of claim 57, wherein the AUC_{0-t} is about 11.1 ng/mL *h.

74. The method of claim 57, wherein the AUC_{0-t} is about 23.7 ng/mL *h.

75. The method of claim 57, wherein the method provides the plasma concentration effective to alleviate the symptoms of Parkinson's disease regardless of where the rotigotine is administered to the body of the human patient.

76. A method of treating Parkinson's Disease in a human patient comprising applying one or more transdermal patches comprising an amount of rotigotine from 4 mg to 20 mg to the patient to provide a plasma concentration effective to alleviate the symptoms of Parkinson's Disease in the human patient, wherein the C_{max} is sustained at a level from about 0.14 ng/mL to about 1.54 ng/mL and the mean area under the curve (AUC_{0-t}) in the patient is from about 3.3 ng/mL *h to about 32.2 ng/mL *h.

77. The method of claim 76, wherein the C_{max} is from about 0.20 ng/mL to about 1.30 ng/mL.

78. The method of claim 76, wherein the C_{max} is from about 0.30 ng/mL to about 1.20 ng/mL.

79. The method of claim 76, wherein the C_{max} is from about 0.14 ng/mL to about 0.48 ng/mL.

80. The method of claim 76, wherein the C_{max} is from about 0.37 ng/mL to about 0.75 ng/mL.

81. The method of claim 76, wherein the C_{max} is from about 0.84 ng/mL to about 1.54 ng/mL.

82. The method of claim 76, wherein the C_{max} is about 0.31 ng/mL.

83. The method of claim 76, wherein the C_{max} is about 0.56 ng/mL.

84. The method of claim 76, wherein the C_{max} is about 1.19 ng/mL.

85. The method of claim 76, wherein the AUC_{0-t} is from about 4.0 ng/mL *h to about 30.0 ng/mL *h.

86. The method of claim 76, wherein the AUC_{0-t} is from about 5.0 ng/mL *h to about 25.0 ng/mL *h.

87. The method of claim 76, wherein the AUC_{0-t} is from about 3.3 ng/mL *h to about 8.9 ng/mL *h.

88. The method of claim 76, wherein the AUC_{0-t} is from about 7 ng/mL *h to about 15.2 ng/mL *h.

89. The method of claim 76, wherein the AUC_{0-t} is from about 15.2 ng/mL *h to about 32.2 ng/mL *h.

90. The method of claim 76, wherein the AUC_{0-t} is about 6.1 ng/mL *h.

91. The method of claim 76, wherein the AUC_{0-t} is about 11.1 ng/mL *h.

92. The method of claim 76, wherein the AUC_{0-t} is about 23.7 ng/mL *h.

93. The method of claim 76, wherein the method provides the plasma concentration effective to alleviate the symptoms of Parkinson's disease regardless of where the rotigotine is administered to the body of the human patient.

94. A method of treating Parkinson's Disease in a human patient comprising

a) applying one or more transdermal patches comprising an amount of rotigotine from 4 mg to 20 mg to the patient;

b) removing the patch or patches of step a) and applying another patch or patches comprising an amount of rotigotine from 4 mg to 20 mg to the patient at an interval providing a plasma concentration effective to alleviate the symptoms of Parkinson's Disease in the patient; and

c) repeating step b) as required to sustain the C_{max} at a level effective to alleviate the symptoms of Parkinson's Disease in the human patient,

wherein the C_{max} is sustained at a level from about 0.14 ng/mL to about 1.54 ng/mL.

95. The method of claim 94, wherein the C_{max} is from about 0.20 ng/mL to about 1.30 ng/mL.

96. The method of claim 94, wherein the C_{max} is from about 0.30 ng/mL to about 1.20 ng/mL.

97. The method of claim 94, wherein the C_{max} is from about 0.14 ng/mL to about 0.48 ng/mL.

98. The method of claim 94, wherein the C_{max} is from about 0.37 ng/mL to about 0.75 ng/mL.

99. The method of claim 94, wherein the C_{max} is from about 0.84 ng/mL to about 1.54 ng/mL.

100. The method of claim 94, wherein the C_{max} is about 0.31 ng/mL.

101. The method of claim 94, wherein the C_{max} is about 0.56 ng/mL.

102. The method of claim 94, wherein the C_{max} is about 1.19 ng/mL.

103. The method of claim 94, wherein the C_{max} is sustained at a level effective to alleviate the symptoms of Parkinson's Disease in the human patient for a period from 1 day to 7 days.

104. The method of claim 94, wherein the C_{max} is sustained at a level effective to alleviate the symptoms of Parkinson's Disease in the human patient for a period of time is from 1 week to 6 weeks.

105. The method of claim 94, wherein the C_{max} is sustained at a level effective to alleviate the symptoms of Parkinson's Disease in the human patient for a period of time is 7 weeks.

106. The method of claim 94, wherein the C_{max} is sustained at a level effective to alleviate the symptoms of Parkinson's Disease in the human patient for a period of time is from 8 weeks to 28 weeks.

107. The method of claim 94, wherein the method gives the plasma concentration effective to alleviate the symptoms of Parkinson's Disease regardless of where the patches are applied on the body of the human patient.

108. The method of claim 94, wherein the patch or patches are replaced daily.

109. The method of claim 94, wherein the C_{max} is sustained at a level effective to alleviate the symptoms of Parkinson's Disease in the human patient for a period of time from 1 day to 28 weeks.

110. A method for treating Parkinson's Disease in a human patient, comprising administering over a 24 hour period a rotigotine formulation capable of providing a plasma concentration effective to alleviate the symptoms of Parkinson's Disease, wherein the C_{max} is from about 0.14 ng/mL to about 1.54 ng/mL and the AUC_{0-t} is from about 3.3 ng/mL *h to about 32.2 ng/mL *h, regardless of where the rotigotine is administered to the body of the human patient.

Figure 1: Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 9.0mg rotigotine with Patch A

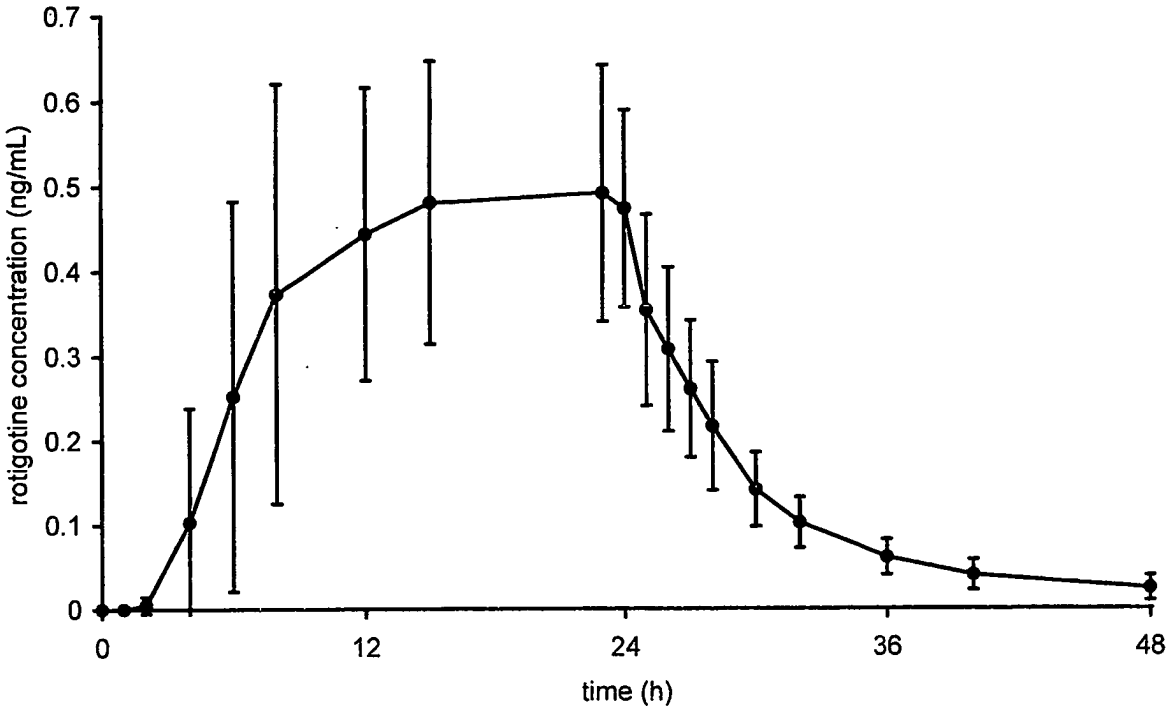


Figure 2: Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 18.0mg rotigotine with 2 x Patch A

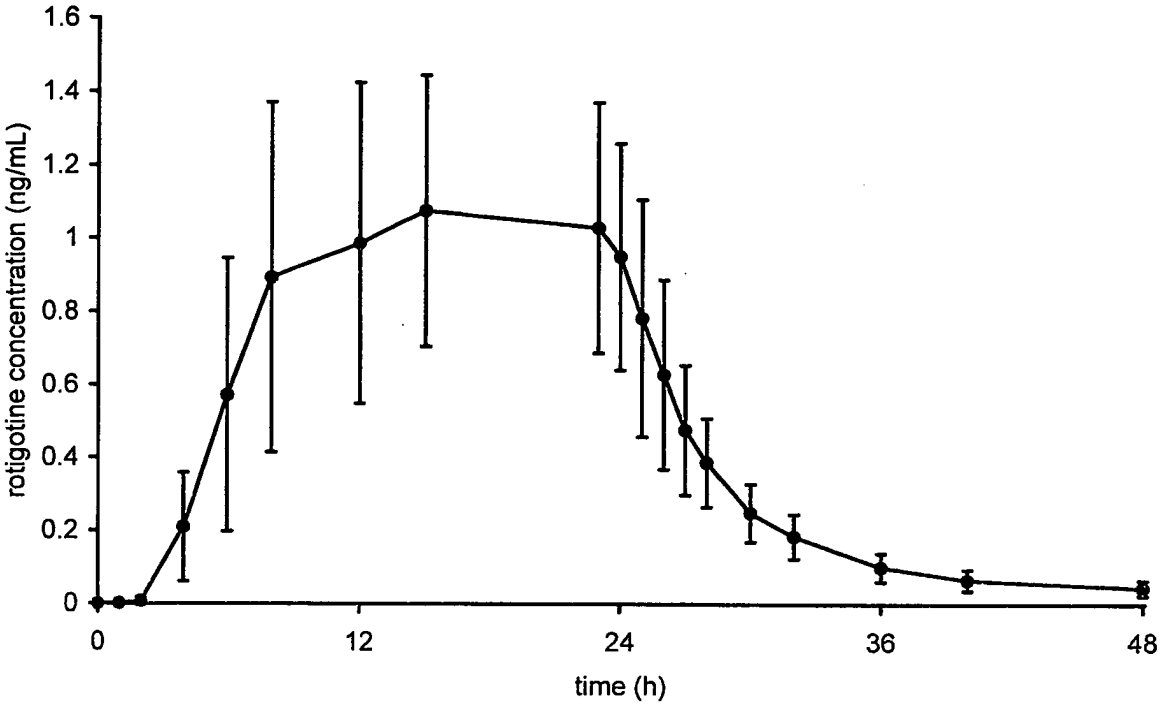


Figure 3: Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 33.48mg rotigotine (state) with Patch B.

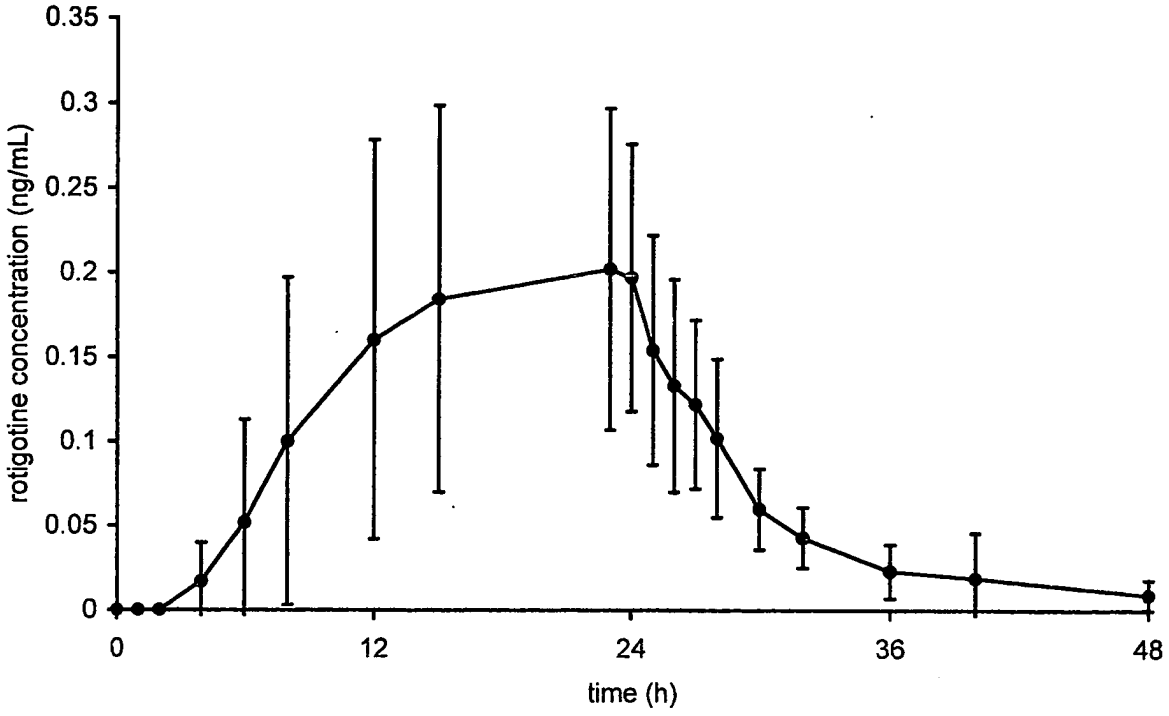


Figure 4: Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after multiple transdermal administration of 4.5mg rotigotine with Patch C

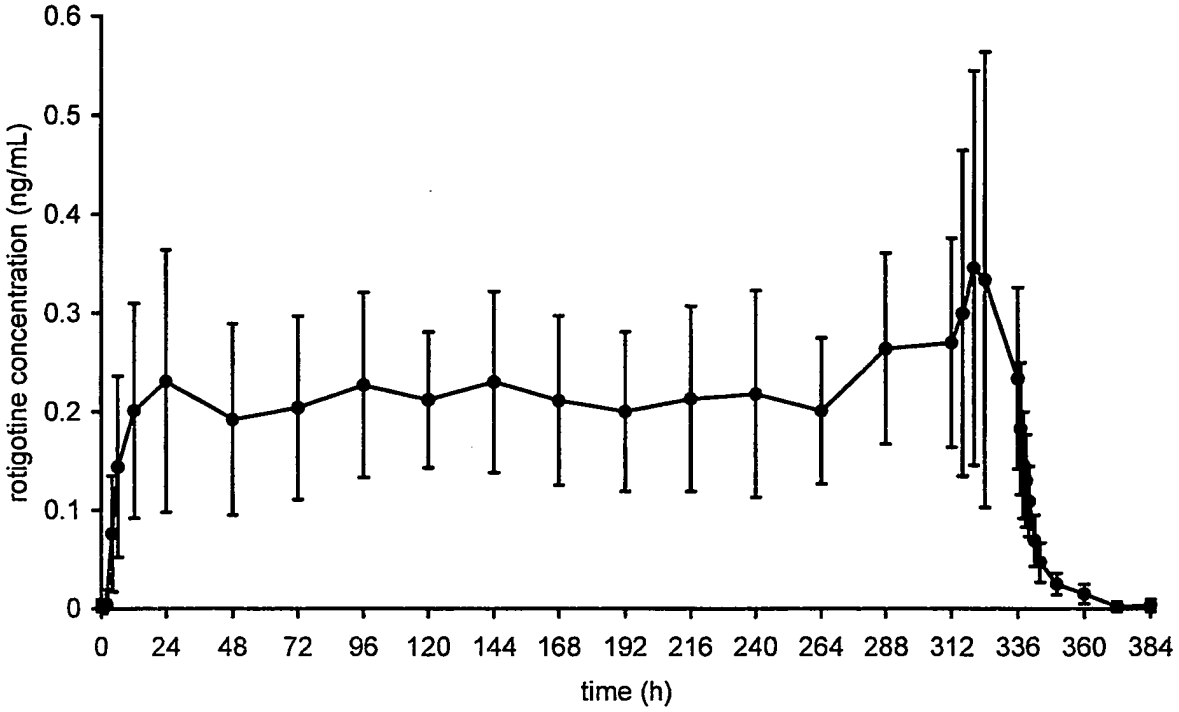


Figure 5: Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after last transdermal administration of 4.5mg rotigotine with Patch C.

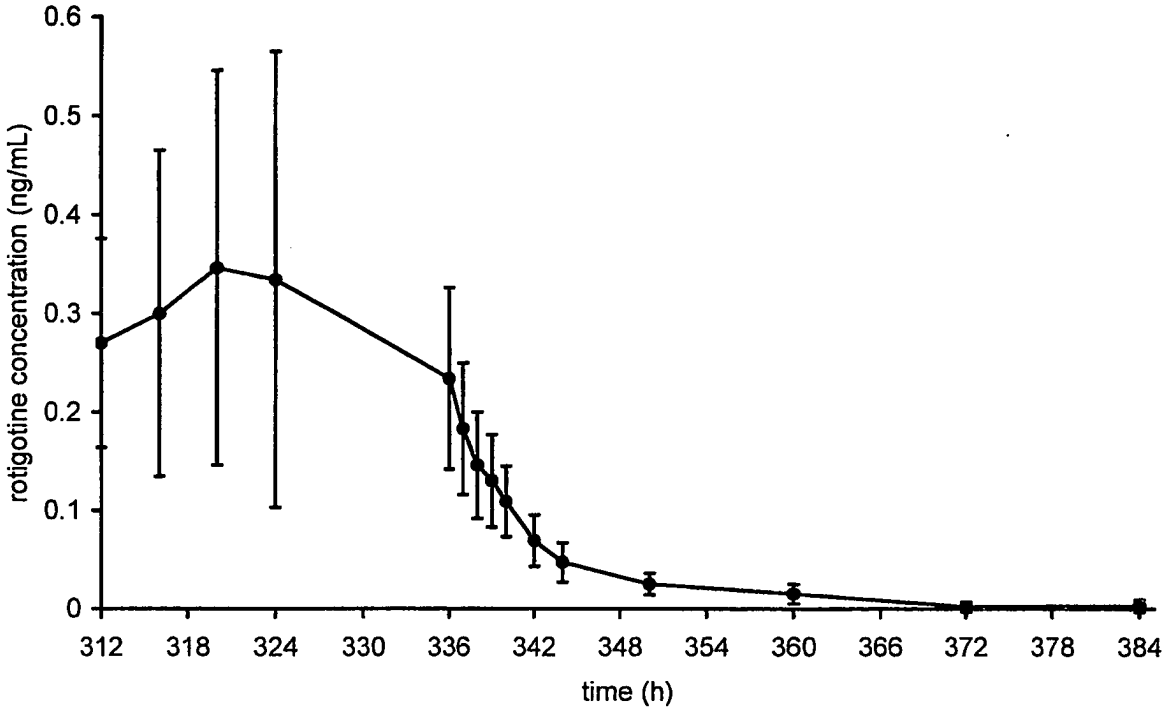


Figure 6: Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 4.5mg rotigotine with Patch D

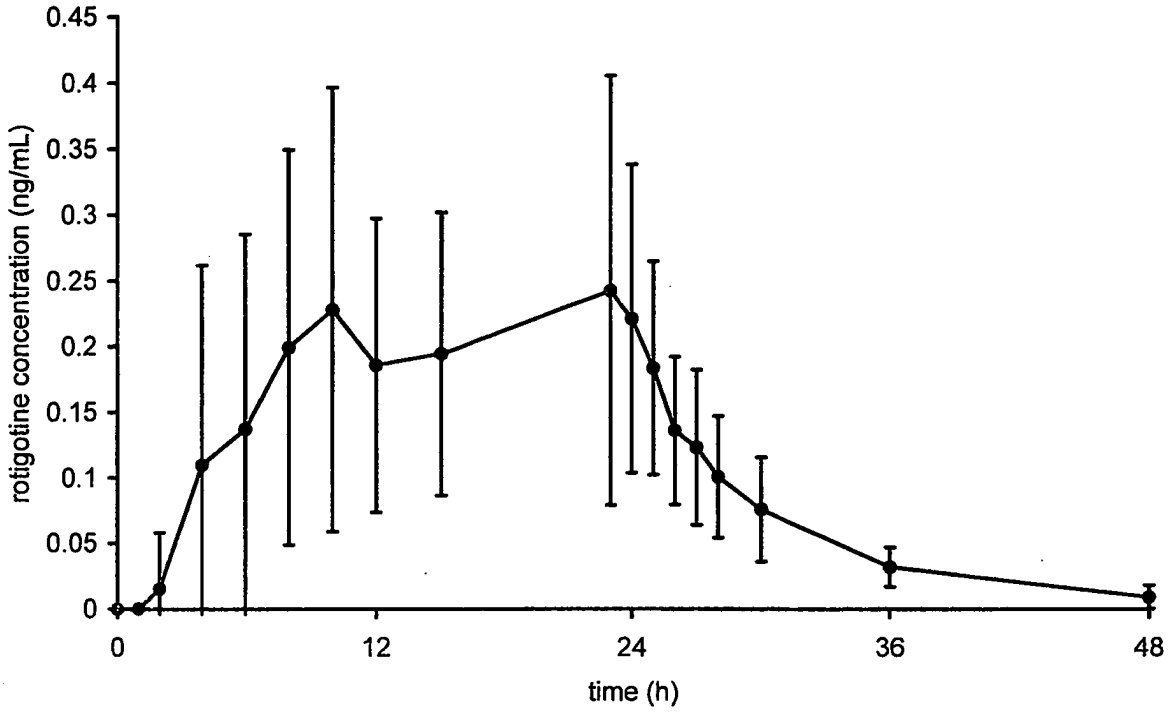


Figure 7: Mean (+/-standard deviation) rotigotine plasma concentrations (in ng/mL) during and after single transdermal administration of 4.5mg rotigotine with Patch C

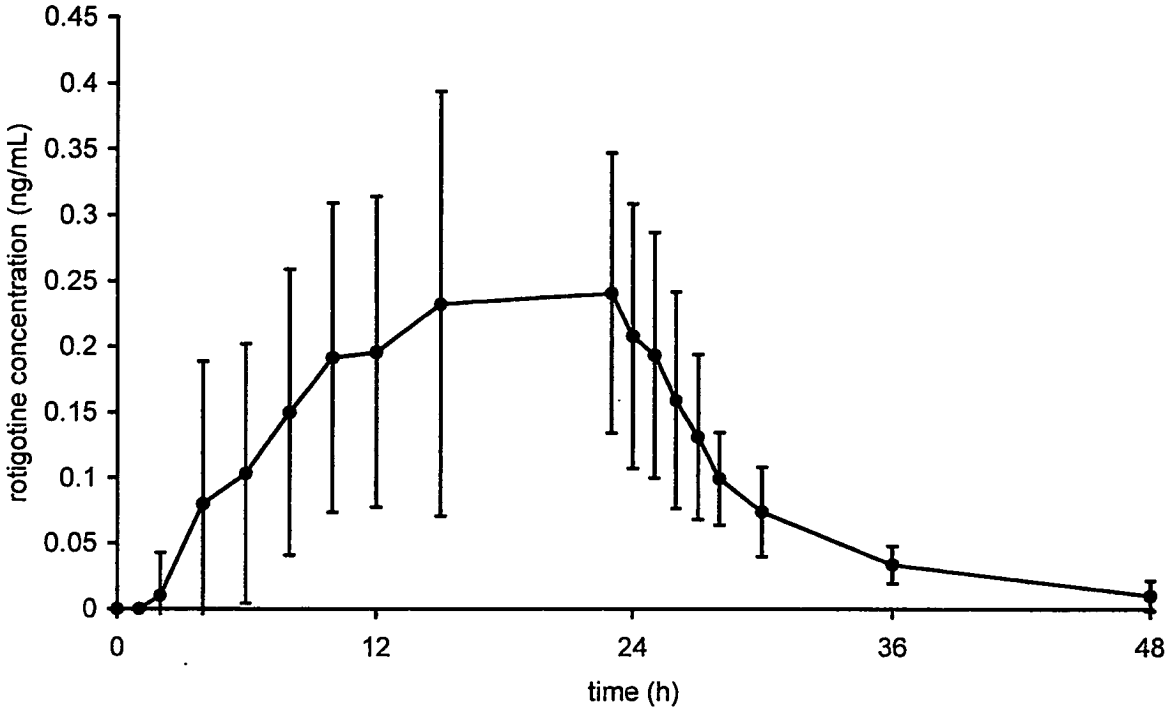


Figure 8: Mean plasma concentrations versus time for each of the six application sites using combined data from Days 27 and 30 (after normalization by body weight and apparent dose)

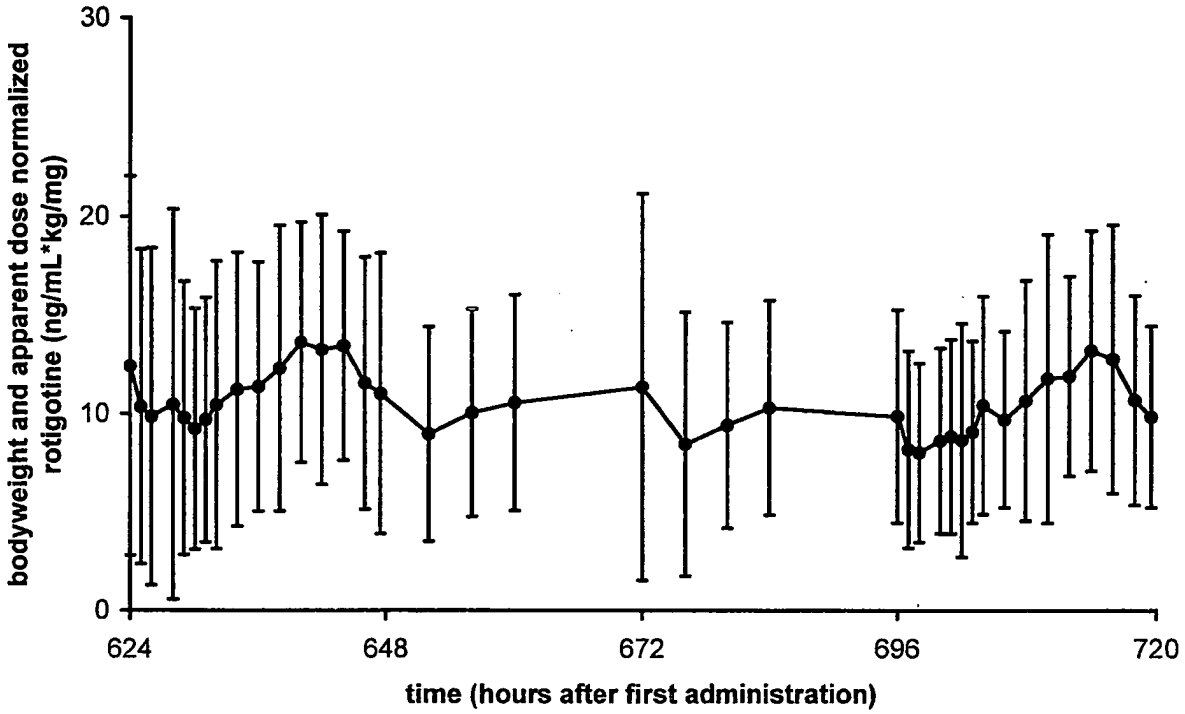


Figure 9: Plasma concentration over time for all patch application sites (after normalization by body weight and apparent dose)

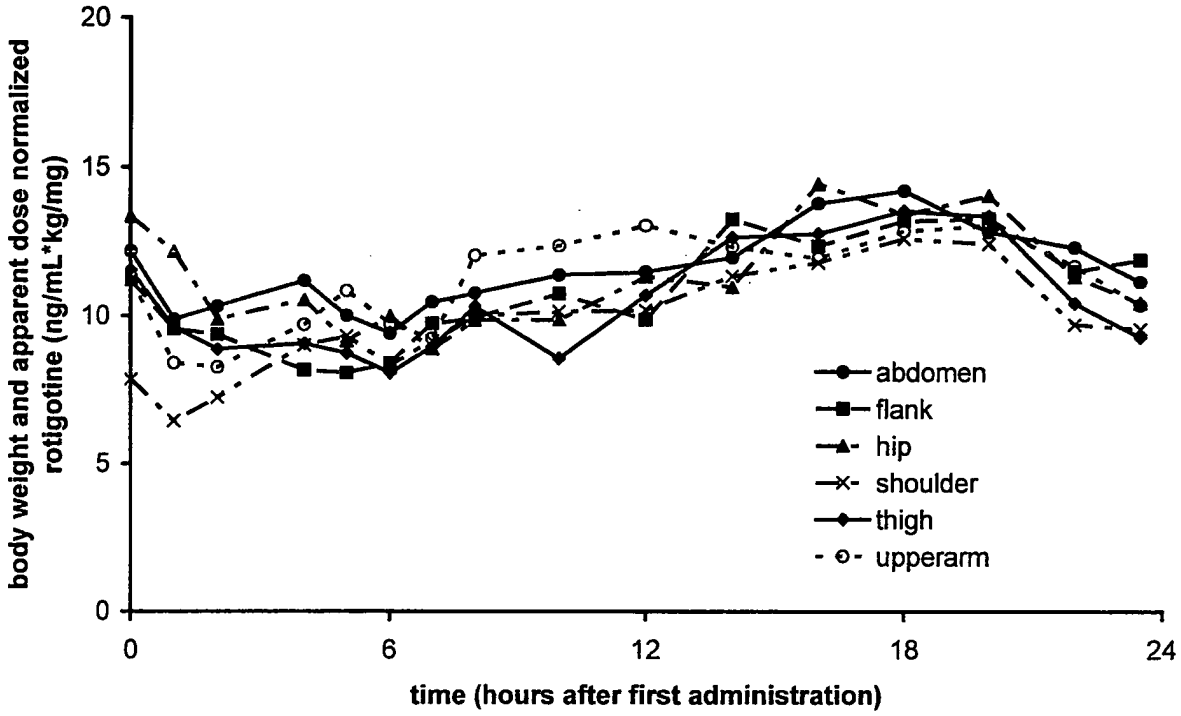


Figure 10: Arithmetic mean and standard deviation of the rotigotine plasma concentrations (ng/mL) during titration and maintenance phase